



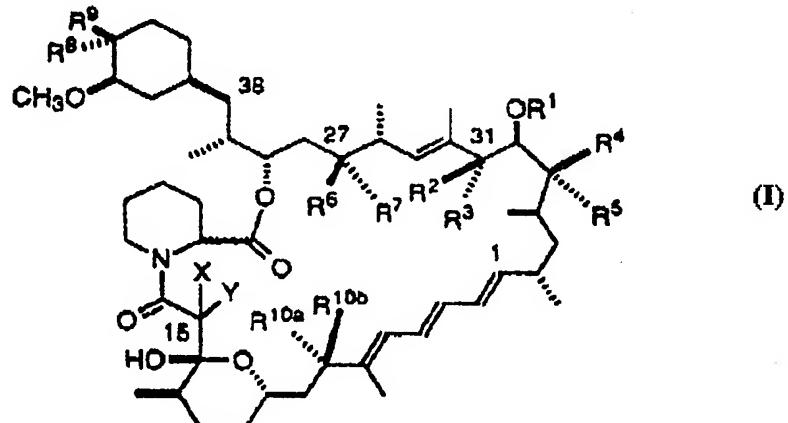
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(54) Title: SEMISYNTHETIC ANALOGS OF RAPAMYCIN (MACROLIDES) BEING IMMUNOMODULATORS

(57) Abstract

Novel macrolide compounds, semisynthetic analogs of Rapamycin, of formula (I) and pharmaceutically acceptable salts, esters, amides and prodrugs thereof, processes for the preparation of the compounds of the invention, intermediates useful in these processes, a pharmaceutical composition, and a method of treating immunomodulatory disorders are disclosed.



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Semisynthetic analogs of Rapamycin (Macrolides) being immunomodulators

10 This is a continuation-in-part of U.S. patent application Serial No. 155,064, filed November 19, 1993.

Technical Field

15 The present invention relates to novel chemical compounds having immunomodulatory activity and synthetic intermediates useful for the preparation of the novel compounds, and in particular to macrolide immunomodulators. More particularly, the invention relates to semisynthetic analogs of rapamycin, means for their preparation, pharmaceutical compositions containing such compounds and methods of treatment employing the same.

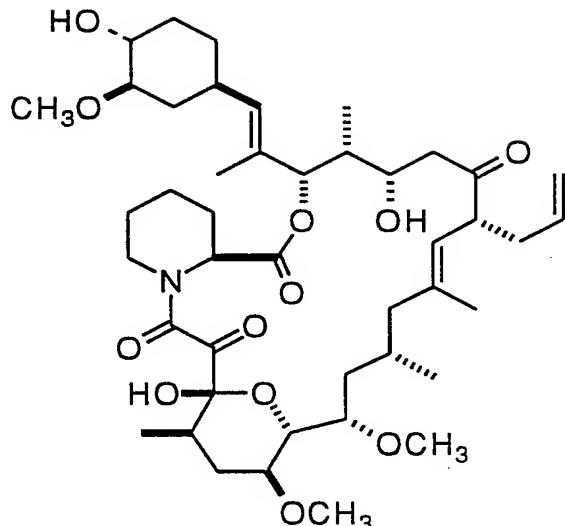
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Background of the Invention

The compound cyclosporine (cyclosporin A) has found wide use since its introduction in the fields of organ transplantation and immunomodulation, and has brought about a significant increase in the success rate for transplantation procedures. Recently, several classes of macrocyclic compounds having potent immunomodulatory activity have been discovered. Okuhara *et al.*, in European Patent Application No. 184,162, published June 11, 1986, disclose a number of macrocyclic compounds isolated from the genus *Streptomyces*.

25 Immunosuppressant FK-506, isolated from a strain of *S. tsukubaensis*, is a 30 23-membered macrocyclic lactone represented by the formula shown below.

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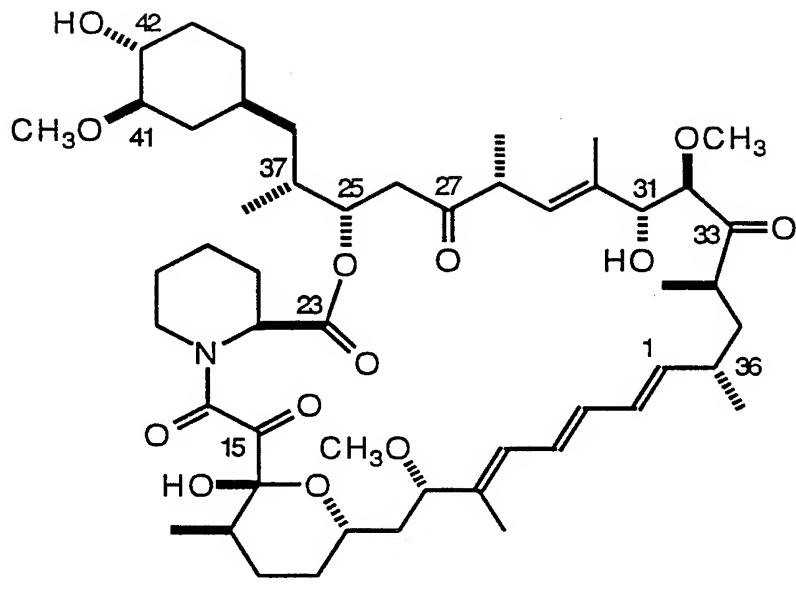


FK-506

- 5 Other related natural products, such as FR-900520 and FR-900523, which differ from FK-506 in their alkyl substituent at C-21, have been isolated from *S. hygroscopicus yakushimaensis*. Yet another analog, FR-900525, produced by *S. tsukubaensis*, differs from FK-506 in the replacement of a pipecolic acid moiety with a proline group. Unsatisfactory side-effects associated with
10 cyclosporine and FK-506 such as nephrotoxicity, have led to a continued search for immunosuppressant compounds having improved efficacy and safety.

Rapamycin is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*, which was found to have antifungal activity, particularly against *Candida albicans*, both in vitro and in vivo (C. Vezina et al., *J. Antibiot.* 1975, 28, 721; S. N. Sehgal et al., *J. Antibiot.* 1975, 28, 727; H. A. Baker et al., *J. Antibiot.* 1978, 31, 539; U.S. Patent No. 3,929,992; and U.S. Patent No. 3,993,749).

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Rapamycin

Rapamycin alone (U.S. Patent No. 4,885,171) or in combination with 5 picibanil (U.S. Patent No. 4,401,653) has been shown to have antitumor activity. In 1977, rapamycin was also shown to be effective as an immunosuppressant in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and was shown to effectively inhibit the formation of IgE-like antibodies (R. Martel 10 et al., *Can. J. Physiol. Pharmacol.*, 1977, 55, 48).

The immunosuppressive effects of rapamycin have also been disclosed in FASEB, 1989, 3, 3411 as has its ability to prolong survival time of organ grafts in histoincompatible rodents (R. Morris, *Med. Sci. Res.*, 1989, 17, 877). The ability of rapamycin to inhibit T-cell activation was disclosed by M. Strauch 15 (FASEB, 1989, 3, 3411). These and other biological effects of rapamycin are reviewed in *Transplantation Reviews*, 1992, 6, 39-87.

Mono-ester and di-ester derivatives of rapamycin (esterification at 20 positions 31 and 42) have been shown to be useful as antifungal agents (U.S. Patent No. 4,316,885) and as water soluble prodrugs of rapamycin (U.S. Patent No. 4,650,803).

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Fermentation and purification of rapamycin and 30-demethoxy rapamycin have been described in the literature (C. Vezina et al. *J. Antibiot.* (Tokyo), 1975, 28 (10), 721; S. N. Sehgal et al., *J. Antibiot.* (Tokyo), 1975, 28(10), 727; 1983, 36(4), 351; N. L. Pavia et al., *J. Natural Products*, 1991, 54(1), 167-177).

Numerous chemical modifications of rapamycin have been attempted. These include the preparation of mono- and di-ester derivatives of rapamycin (WO 92/05179), 27-oximes of rapamycin (EP0 467606); 42-oxo analog of rapamycin (U.S. Patent No. 5,023,262); bicyclic rapamycins (U.S. Patent No. 10 5,120,725); rapamycin dimers (U.S. Patent No. 5,120,727); silyl ethers of rapamycin (U.S. Patent No. 5,120,842); and arylsulfonates and sulfamates (U.S. Patent No. 5,177, 203). Rapamycin was recently synthesized in its naturally occurring enantiomeric form (K. C. Nicolaou et al., *J. Am. Chem. Soc.*, 1993, 115, 4419-4420; S. L. Schreiber, *J. Am. Chem. Soc.*, 1993, 115, 7906-7907; S. J. 15 Danishefsky, *J. Am. Chem. Soc.*, 1993, 115, 9345-9346.

It has been known that rapamycin, like FK-506, binds to FKBP-12 (Siekierka, J. J.; Hung, S. H. Y.; Poe, M.; Lin, C. S.; Sigal, N. H. *Nature*, 1989, 341, 755-757; Harding, M. W.; Galat, A.; Uehling, D. E.; Schreiber, S. L. *Nature* 1989, 341, 758-760; Dumont, F. J.; Melino, M. R.; Staruch, M. J.; Koprak, S. L.; 20 Fischer, P. A.; Sigal, N. H. *J. Immunol.* 1990, 144, 1418-1424; Bierer, B. E.; Schreiber, S. L.; Burakoff, S. J. *Eur. J. Immunol.* 1991, 21, 439-445; Fretz, H.; Albers, M. W.; Galat, A.; Standaert, R. F.; Lane, W. S.; Burakoff, S. J.; Bierer, B. E.; Schreiber, S. L. *J. Am. Chem. Soc.* 1991, 113, 1409-1411). Recently it has been discovered that the rapamycin/FKBP-12 complex binds to yet another 25 protein, which is distinct from calcineurin, the protein that the FK-506/FKBP-12 complex inhibits (Brown, E. J.; Albers, M. W.; Shin, T. B.; Ichikawa, K.; Keith, C. T.; Lane, W. S.; Schreiber, S. L. *Nature* 1994, 369, 756-758.; Sabatini, D. M.; Erdjument-Bromage, H.; Lui, M.; Tempest, P.; Snyder, S. H. *Cell*, 1994, 78, 35-43).

30 Although some of these modified compounds exhibit immunosuppressive activity, the need remains for macrocyclic immunosuppressants which do not have the serious side effects frequently associated with immunosuppressant therapy. Accordingly, one object of this invention is to provide novel

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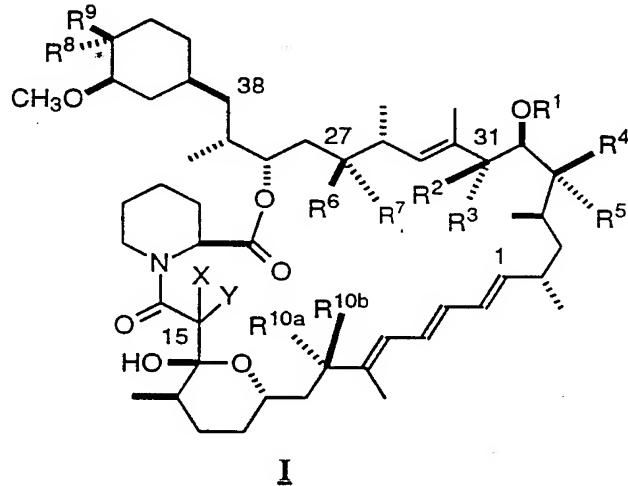
semisynthetic macrolides which possess the desired immunomodulatory activity but which may be found to minimize untoward side effects.

Another object of the present invention is to provide synthetic processes for the preparation of such compounds from starting materials obtained by
5 fermentation, as well as chemical intermediates useful in such synthetic processes.

A further object of the invention is to provide pharmaceutical compositions containing, as an active ingredient, at least one of the above compounds. Yet another object of the invention is to provide a method of
10 treating a variety of disease states, including post-transplant tissue rejection and autoimmune dysfunction.

Disclosure of the Invention

In one aspect of the present invention there are compounds of the formula
15 I:



wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;
20

R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

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R^4 is hydrogen or phenyl-substituted loweralkyl and R^5 is hydroxy or protected hydroxy or R^5 is hydrogen or phenyl-substituted loweralkyl and R^4 is hydroxy or protected hydroxy or R^4 and R^5 taken together are oxo;

5 R^6 is hydrogen or phenyl-substituted loweralkyl and R^7 is hydrogen, hydroxy or protected hydroxy or R^7 is hydrogen or phenyl-substituted loweralkyl and R^6 is hydroxy or protected hydroxy or R^6 and R^7 taken together are

- (1) oxo,
- (2) diazo,
- 10 (3) $=CH_2$
- (4) $-O-(CH_2)_2-O-$,
- (5) $-S-(CH_2)_2-S-$,
- (6) $-O-(CH_2)_3-O-$,
- (7) $-S-(CH_2)_3-S-$,

15 (8) $=N-OR^{20}$ wherein R^{20} is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

20 (9) $=N-N(R^{21})(R^{22})$ wherein R^{21} and R^{22} are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R^8 is hydrogen;

25 R^9 is

- (1) $-OS(O)_2CF_3$,
- (2) $-OS(O)_2F$,
- (3) $-OS(O)_2R^{21a}$ wherein R^{21a} is loweralkyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl,
- 30 (4) $-OC(O)R^{23}$ wherein R^{23} is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclicalkyl, alkoxy, $-O$ -cycloalkyl, $-O$ -aryl, $-O$ -heterocyclic, $-O$ -(N -succinimidyl) or 5-tetrazolyl;

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(5) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from

- (a) hydrogen,
- (b) loweralkyl,
- 5 (c) alkenyl,
- (d) alkynyl,
- (e) cycloalkyl,

10 (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

- (i) hydroxy,
- (ii) -COOH,
- 15 (iii) -CN,
- (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- (v) cycloalkyl,
- 20 (vi) aryl,
- (vii) heterocyclic,
- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 25 (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,

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- (xiii) -S(O)₂NH₂,
- (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- (xv) halogen,
- (xvi) oxo and
- 5 (xvii) epoxy;
- (g) aryl,
- (h) heterocyclic,
- (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- 10 (k) -NHC(O)-heterocyclic and
- (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- 15 (6) -OR²⁵ wherein R²⁵ is as defined above,
- (7) a protected hydroxy group,
- (8) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (9) -O(CH₂)_iC(O)OR²⁰ wherein i is one or two and R²⁰ is independently defined as above,
- 20 (10) -O(CH(Si(CH₃)₃))-(CH₂)_jC(O)OR²⁰ wherein j is zero or one and R²⁰ is independently defined as above,
- (11) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (12) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- 25 (13) -O(CH₂)_iC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
- (14) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- 30 (15) -O(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (16) -O(CH₂)_iNHC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,

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- (17) -OS(O)₂N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (18) -O(CH₂)_i-NHC(O)R²⁴ wherein R²⁴ is defined as above,
- (19) -OCH(R²⁴)-SH wherein R²⁴ is defined as above,
- (20) -OCH(R²⁴)-S-loweralkyl wherein R²⁴ is defined as above,
- 5 (21) -OCH(R²⁴)-S-aryl wherein R²⁴ is defined as above and
- (22) -N₃;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

15 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

20

Preferred compounds of the formula I are those wherein:

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

25 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ are defined as above;

R⁸ is hydrogen;

R⁹ is defined as above;

30 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

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More preferred compounds of the formula I are those wherein:

- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are
- (1) oxo,
 - (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
10 heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
 - (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- 15 R⁸ is hydrogen;
- R⁹ is
- (1) -OH,
 - (2) -OC(O)R²³ wherein R²³ is -O-aryl, -O-(N-succinimidyl), -O-benzotriazolyl, -O-2'-pyridyl or 5-tetrazolyl,
20 (3) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from
 - (a) hydrogen,
 - (b) loweralkyl,
 - (c) alkenyl,
 - 25 (d) alkynyl,
 - (e) cycloalkyl,
 - (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
 - (i) hydroxy,
 - (ii) -COOH,
 - (iii) -CN,
- 30

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- 5

(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,

10 (v) cycloalkyl,

(vi) aryl,

(vii) heterocyclic,

(viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,

15 (ix) guanidino,

(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,

(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,

(xii) -SO₃H,

(xiii) -S(O)₂NH₂,

20 (xiv) -SR²⁸ wherein R²⁸ is defined as above,

(xv) halogen,

(xvi) oxo and

(xvii) epoxy;

25 (g) aryl,

(h) heterocyclic,

(i) -NHC(O)-O-loweralkyl,

(j) -NHC(O)-aryl,

(k) -NHC(O)-heterocyclic and

(l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl

30 or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,

(4) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,

(5) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are defined as above.

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(6) $-\text{O}(\text{CH}_2)_i\text{C}(\text{O})\text{N}(\text{OR}^{24})(\text{R}^{25})$ wherein i, R²⁴ and R²⁵ are defined as above,

(7) $-\text{O}(\text{CH}_2)_i\text{NHC(O)N}(\text{R}^{24})(\text{R}^{25})$ wherein i, R²⁴ and R²⁵ are defined as above or

5 (8) $-\text{O}(\text{CH}_2)_i\text{NHC(O)N}(\text{OR}^{24})(\text{R}^{25})$ wherein i, R²⁴ and R²⁵ are defined as above;

R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

10 Even more preferred compounds of the formula I are those wherein:

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ taken together are

15 (1) oxo,

(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

20 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

R⁹ is

25 (1) -OH,

(2) -OC(O)R²³ wherein R²³ is -O-aryl, -O-(N-succinimidyl), -O-benzotriazolyl, -O-2'-pyridyl or 5-tetrazolyl,

(3) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from

30 (a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,

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- (e) cycloalkyl,

(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

 - (i) hydroxy,
 - (ii) -COOH,
 - (iii) -CN,
 - (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
 - (v) cycloalkyl,
 - (vi) aryl,
 - (vii) heterocyclic,
 - (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
 - (ix) guanidino,
 - (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
 - (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
 - (xii) -SO₃H,
 - (xiii) -S(O)₂NH₂,
 - (xiv) -SR²⁸ wherein R²⁸ is defined as above,
 - (xv) halogen,
 - (xvi) oxo and
 - (xvii) epoxy;
 - (g) aryl,
 - (h) heterocyclic,
 - (i) -NHC(O)-O-loweralkyl,
 - (j) -NHC(O)-aryl,

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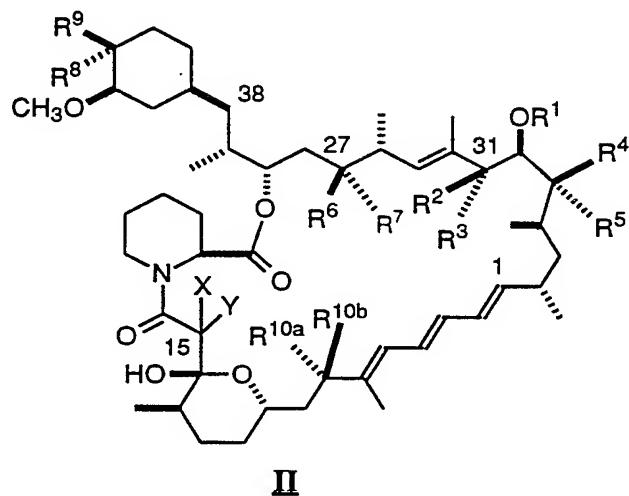
- (k) -NHC(O)-heterocyclic and
(l) loweralkyl substituted by -OC(O)-R^f wherein R^f is
carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing
heterocyclic group,
5 (4) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
(5) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵
are defined as above,
10 (6) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as
above,
(7) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as
above or
(8) -O(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as
above;
15 R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

Most preferred compounds of the formula I are those wherein:

- R¹ is methyl;
20 R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are oxo;
R⁸ is hydrogen;
R⁹ is -OH, -O-loweralkyl or -OC(O)N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are
25 defined as above;
R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

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In another aspect of the present invention there are compounds of the formula II:



- 5 wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;
- 10 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;
- 15 R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;
- 20 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are
 - (1) oxo,
 - (2) diazo,
 - (3) =CH₂,
 - (4) -O-(CH₂)₂-O-,
 - (5) -S-(CH₂)₂-S-,
 - (6) -O-(CH₂)₃-O-,
 - (7) -S-(CH₂)₃-S-,

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(8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

5 (9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

10

R⁹ is

(1) -SR²⁴ wherein R²⁴ is

- (a) hydrogen,
- (b) loweralkyl,
- (c) alkenyl,
- (d) alkynyl,
- (e) cycloalkyl,

15

(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

- (i) hydroxy,
- (ii) -COOH,
- (iii) -CN,

20

(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-,

25

-N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,

- (v) cycloalkyl,
- (vi) aryl,

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- (vii) heterocyclic,
- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 5 (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- (xiii) -S(O)₂NH₂,
- 10 (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- (xv) halogen,
- (xvi) oxo and
- (xvii) epoxy;
- (g) aryl,
- 15 (h) heterocyclic,
- (i) -C(O)-O-loweralkyl,
- (j) -C(O)-aryl,
- (k) -C(O)-heterocyclic or
- (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl,
- 20 (2) -SC(=NH)-NH₂,
- (3) -SC(=N-NH₂)-NH₂,
- (4) -Se-phenyl or
- (5) -Se(O)-phenyl;
- 25 R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and
- 30 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

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or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

5 Preferred compounds of the formula **II** are those wherein:

- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
- 10 R⁶ and R⁷ are defined as above;
- R⁸ is hydrogen;
- R⁹ is -SR²⁴ wherein R²⁴ is defined as above;
- R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
- X and Y taken together are oxo.

15

More preferred compounds of the formula **II** are those wherein:

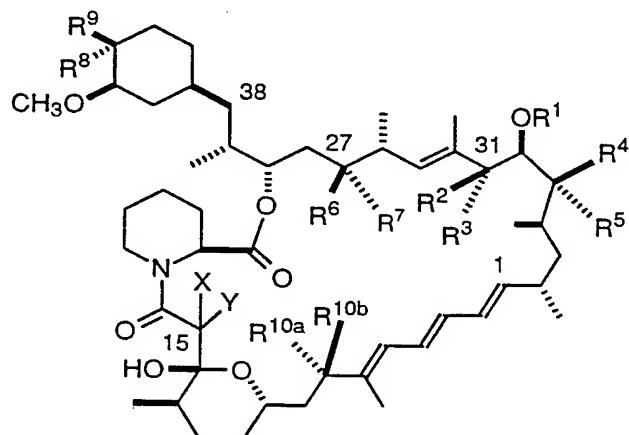
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are
- (1) oxo,
 - (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- 25 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- R⁸ is hydrogen;
- R⁹ is -SR²⁴ wherein R²⁴ is hydrogen, loweralkyl, substituted loweralkyl as defined above, aryl or heterocyclic;
- 30 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
- X and Y taken together are oxo.

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- Even more preferred compounds of the formula **II** are those wherein:
- R¹ is methyl;
 - R² is hydrogen and R³ is hydroxy;
 - 5 R⁴ and R⁵ taken together are oxo;
 - R⁶ and R⁷ taken together are oxo;
 - R⁸ is hydrogen;
 - R⁹ is -SR²⁴ wherein R²⁴ is hydrogen, loweralkyl, substituted loweralkyl as defined above, aryl or heterocyclic;
 - 10 R^{10a} is methoxy and R^{10b} is hydrogen; and
 - X and Y taken together are oxo.

- Most preferred compounds of the formula **II** are those wherein:
- R¹ is methyl;
 - 15 R² is hydrogen and R³ is hydroxy;
 - R⁴ and R⁵ taken together are oxo;
 - R⁶ and R⁷ taken together are oxo;
 - R⁸ is hydrogen;
 - R⁹ is -SR²⁴ wherein R²⁴ is hydrogen, imidazol-2-yl or N-methyl-imidazol-2-yl;
 - 20 R^{10a} is methoxy and R^{10b} is hydrogen; and
 - X and Y taken together are oxo.

In another aspect of the present invention there are compounds of the formula **III**:



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wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

5 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

10

R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

15

(1) oxo,

(2) diazo,

(3) =CH₂

(4) -O-(CH₂)₂-O-,

(5) -S-(CH₂)₂-S-,

(6) -O-(CH₂)₃-O-,

20

(7) -S-(CH₂)₃-S-,

(8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

25

(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

30

R⁹ is

(1) -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from
(a) hydrogen,

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- (b) loweralkyl,
- (c) alkenyl,
- (d) alkynyl,
- (e) cycloalkyl,
- 5 (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
 - (i) hydroxy,
 - (ii) -COOH,
 - 10 (iii) -CN,
 - (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
 - 15 (v) cycloalkyl,
 - (vi) aryl,
 - (vii) heterocyclic,
 - (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
 - 20 (ix) guanidino,
 - (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
 - (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
 - (xii) -SO₃H,
 - (xiii) -S(O)₂NH₂,
 - 25 (xiv) -SR²⁸ wherein R²⁸ is defined as above,
 - (xv) halogen,
 - (xvi) oxo and
 - (xvii) epoxy;
- 30 (g) aryl,

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- (h) heterocyclic,
- (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- (k) -NHC(O)-heterocyclic and
- 5 (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl,
- (2) -N=C=O,
- (3) -NHC(O)-R* or
- (4) -NHS(O)₂-R* wherein R* is
- 10 (a) loweralkyl,
- (b) cycloalkyl,
- (c) aryl,
- (d) heterocyclic,
- (e) loweralkyl substituted by one or two substituents
- 15 independently selected from
 - (i) hydroxy,
 - (ii) -COOH,
 - (iii) -CN,
 - (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
 - 20 R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
 - (v) cycloalkyl,
 - (vi) aryl,
 - (vii) heterocyclic,
 - (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
 - 25 (ix) guanidino,
 - (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
 - (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- 30

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(xii) SO_3H ,

(xiii) $\text{S(O)}_2\text{NH}_2$,

(xiv) $-\text{SR}^{28}$ wherein R^{28} is defined as above,

(xv) halogen,

5 (xvi) oxo and

(xvii) epoxy;

(f) $-\text{N}(\text{R}^a)(\text{R}^b)$ wherein R^a and R^b are independently selected from hydrogen, loweralkyl and $-\text{N}(\text{R}^c)(\text{R}^d)$ wherein R^c and R^d are independently selected from hydrogen and loweralkyl or

10 (g) $-\text{OR}^*$ wherein R^* is defined as above;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

15 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

20 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

25 Preferred compounds of the formula III are those wherein:

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;

30 R⁶ and R⁷ are defined as above;

R⁸ is hydrogen;

R⁹ is $-\text{N}(\text{R}^{24})(\text{R}^{25})$ wherein R²⁴ and R²⁵ are defined as above;

R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and

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X and Y taken together are oxo.

More preferred compounds of the formula **III** are those wherein:

- R¹ is methyl;
- 5 R² is hydrogen and R³ is hydroxy;
- R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are
- 10 (1) oxo,
- (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
- 15 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- R⁸ is hydrogen;
- R⁹ is -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from hydrogen, loweralkyl, substituted loweralkyl as defined above,
- 20 -NHC(O)-O-loweralkyl, -NHC(O)-aryl and -NHC(O)-heterocyclic or R²⁴ and R²⁵ taken together form a heterocyclic ring;
- R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
- X and Y taken together are oxo.
- 25 Even more preferred compounds of the formula **III** are those wherein:
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are oxo;
- 30 R⁸ is hydrogen;
- R⁹ is -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from hydrogen, loweralkyl, substituted loweralkyl as defined above,
- NHC(O)-O-loweralkyl, -NHC(O)-aryl and -NHC(O)-heterocyclic or R²⁴ and R²⁵ taken together form a heterocyclic ring;

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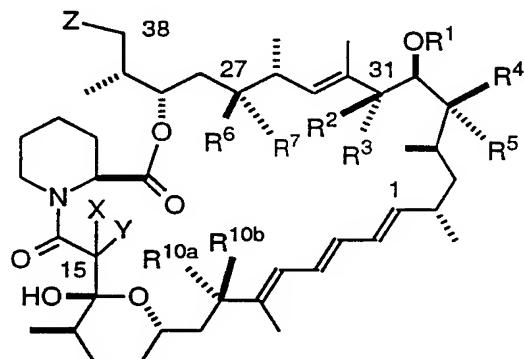
R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

Most preferred compounds of the formula III are those wherein:

- 5 R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are oxo;
- R⁸ is hydrogen;
- 10 R⁹ is -NH₂, 2-pyridon-1-yl or 4-pyridon-1-yl;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
- X and Y taken together are oxo.

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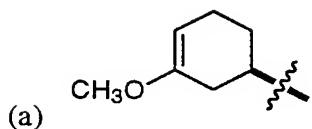
In another aspect of the present invention there are compounds of the formula IV:



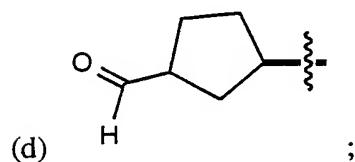
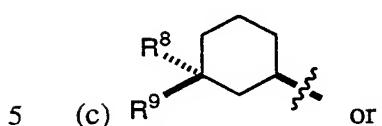
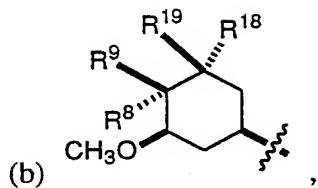
IV

20

wherein Z is



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R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

15

R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

20

R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

25

R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

(1) oxo,

25

(2) diazo,

(3) =CH₂

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- (4) -O-(CH₂)₂-O-,
 - (5) -S-(CH₂)₂-S-,
 - (6) -O-(CH₂)₃-O-,
 - (7) -S-(CH₂)₃-S-,
- 5 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- 10 (9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

- R⁸, R⁹, R¹⁸ and R¹⁹ are independently selected from
- (1) hydrogen,
 - (2) -OS(O)₂CF₃,
 - (3) -OS(O)₂F,
 - (4) -OS(O)₂R^{21a} wherein R^{21a} is loweralkyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl,
 - (5) -OC(O)R²³ wherein R²³ is -O-aryl, -O-(N-succinimidyl), -O-benzotriazolyl, -O-2'-pyridyl or 5-tetrazolyl;
 - 20 (6) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from
 - (a) hydrogen,
 - (b) loweralkyl,
 - (c) alkenyl,
 - (d) alkynyl,
 - (e) cycloalkyl,
 - (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
 - (i) hydroxy,
 - (ii) -COOH,

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- (iii) -CN,
- (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 5 (v) cycloalkyl,
- 10 (vi) aryl,
- (vii) heterocyclic,
- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 15 (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- (xiii) -S(O)₂NH₂,
- 20 (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- (xv) halogen,
- (xvi) oxo and
- (xvii) epoxy;
- 25 (g) aryl,
- (h) heterocyclic,
- (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- (k) -NHC(O)-heterocyclic and
- (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
- 30 or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- (7) -OR²⁵ wherein R²⁵ is as defined above,
- (8) a protected hydroxy group,

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- (9) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (10) -O(CH₂)_iC(O)OR²⁰ wherein i is one or two and R²⁰ is independently defined as above,
- 5 (11) -O(CH(Si(CH₃)₃))-(CH₂)_jC(O)OR²⁰ wherein j is zero or one and R²⁰ is independently defined as above,
- (12) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- 10 (13) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (14) -O(CH₂)_iC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
- 15 (15) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (16) -O(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- 20 (17) -O(CH₂)_iNHC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
- (18) -OS(O)₂N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (19) -O(CH₂)_i-NHC(O)R²⁴ wherein R²⁴ is defined as above,
- 25 (20) -OCH(R²⁴)-SH wherein R²⁴ is defined as above,
- (21) -OCH(R²⁴)-S-loweralkyl wherein R²⁴ is defined as above,
- (22) -OCH(R²⁴)-S-aryl wherein R²⁴ is defined as above,
- (23) -N₃,
- (24) -N=C=O,
- 30 (25) -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (26) -NHC(O)-R²⁴ wherein R²⁴ is defined as above,
- (27) -NHC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (28) -S-R²⁴ wherein R²⁴ is defined as above and
- (29) -S-q-R²⁴ wherein q is a divalent radical selected from the group consisting of -S-, -C(O)-, -C(O)-O-, -C(O)-NH- and -C(N(R²⁷))-NHNH- and R²⁴ and R²⁷ are defined as above,

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with the proviso that one of R⁸ and R⁹ is hydrogen and the other is not hydrogen and one of R¹⁸ and R¹⁹ is hydrogen and the other is not hydrogen; or

R⁸ and R⁹ taken together are

- 5 (1) oxo,
 (2) =N-O-R²⁴ wherein R²⁴ is defined as above or
 (3) =N-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above; or

R¹⁸ and R¹⁹ taken together are

- 10 (1) oxo,
 (2) =N-O-R²⁴ wherein R²⁴ is independently defined as above or
 (3) =N-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently defined as above; or

one of R⁸ and R⁹ taken together with one of R¹⁸ and R¹⁹ form a heterocyclic ring with the others of R⁸, R⁹, R¹⁸ and R¹⁹ being hydrogen or together forming a bond; or

R⁸ and R¹⁸ are hydrogen and R^{8'} and R¹⁹ form a bond;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

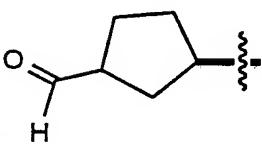
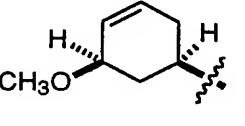
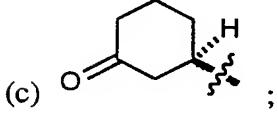
25 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

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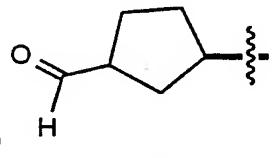
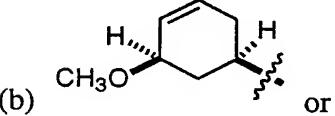
Preferred compounds of the formula IV are those wherein:

Z is

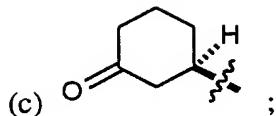
- 5 (a) 
- (b)  or
- 10 (c) 
- 15 R¹ is methyl;
 R² is hydrogen and R³ is hydroxy;
 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
 R⁵ taken together are oxo;
 R⁶ and R⁷ are defined as above;
 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
 X and Y taken together are oxo.

More preferred compounds of the formula IV are those wherein:

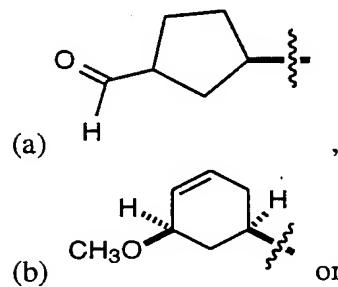
Z is

- 20 (a) 
- (b) 

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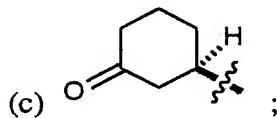


- R¹ is methyl;
- 5 R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
- (1) oxo,
- 10 (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
- 15 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;
- R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.
- 20 Even more preferred compounds of the formula IV are those wherein:
Z is



25

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R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

5 R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ taken together are

(1) oxo,

(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or

10 heterocyclical alkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclical alkyl;

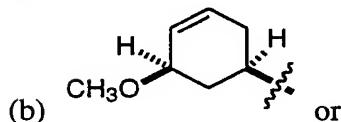
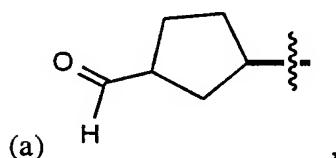
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R^{10a} is methoxy and R^{10b} is hydrogen; and

X and Y taken together are oxo.

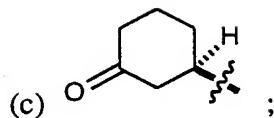
Most preferred compounds of the formula IV are those wherein:

20 Z is



25

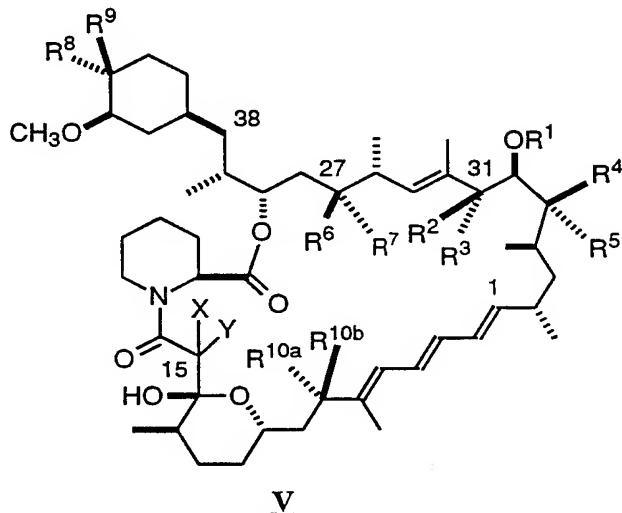
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- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- 5 R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are oxo;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
- X and Y taken together are oxo.

10

In another aspect of the present invention there are compounds of the formula V:



15

wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

- 20 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

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R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R₅ taken together are oxo;

5 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

- (1) oxo,
- (2) diazo,
- 10 (3) =CH₂
- (4) -O-(CH₂)₂-O-,
- (5) -S-(CH₂)₂-S-,
- (6) -O-(CH₂)₃-O-,
- (7) -S-(CH₂)₃-S-,

15 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected

20 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is

- 25 (1) -OC(O)N(OR²⁰)(R²⁴) or
(2) -O-C(O)-NHN(R²⁴)(R²⁵)
wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl or heterocyclic, each of which is optionally substituted with loweralkyl, hydroxy, aryl or heterocyclic and R²⁴ and R²⁵ are independently selected from
- 30 (a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,

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- (e) cycloalkyl,
(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl
or substituted cycloalkyl wherein the loweralkyl group, the
alkenyl group, the alkynyl group or the cycloalkyl group is
5 substituted by one or two substituents independently selected from
(i) hydroxy,
(ii) -COOH,
(iii) -CN,
(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic
10 or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-,
-S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-,
-O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,
-NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-,
-N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
15 R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
(v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
(viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently
20 selected from hydrogen, loweralkyl, hydroxyalkyl, aryl
and heterocyclic,
(ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
25 (xii) -SO₃H,
(xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
(xvi) oxo and
30 (xvii) epoxy;
(g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,

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- (k) -NHC(O)-heterocyclic or
(l) loweralkyl substituted by -OC(O)-R^f wherein R^f is
carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing
heterocyclic group;

5

R⁹ is hydrogen;

- 10 R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy,
alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as
above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy,
alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently
defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is
loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and
15
- 15 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen
and X is hydroxy or protected hydroxy or X and Y taken together are oxo;
20 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

20

Preferred compounds of the formula V are those wherein:

- 25 R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is defined as above;
R⁹ is hydrogen;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen;
30 R²⁰ is defined as above;
R²⁴ is defined as above; and
X and Y taken together are oxo.

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More preferred compounds of the formula V are those wherein:

- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R₅ taken together are oxo;
- 5 R⁶ and R⁷ taken together are
 - (1) oxo,
 - (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or 10 heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
 - (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- 15 R⁸ is -OC(O)N(OR²⁰)(R²⁴) wherein R²⁰ and R²⁴ are defined as above; R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

Even more preferred compounds of the formula V are those wherein:

- 20 R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are oxo;
- R⁸ is -OC(O)N(OR²⁰)(R²⁴) wherein R²⁰ is hydrogen, loweralkyl or arylalkyl and 25 R²⁴ is hydrogen, loweralkyl or cycloalkyl;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
- X and Y taken together are oxo.

Most preferred compounds of the formula V are those wherein:

- 30 R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are oxo;

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R⁸ is -OC(O)N(OR²⁰)(R²⁴) wherein R²⁰ is hydrogen, methyl or benzyl and R²⁴ is hydrogen or methyl;

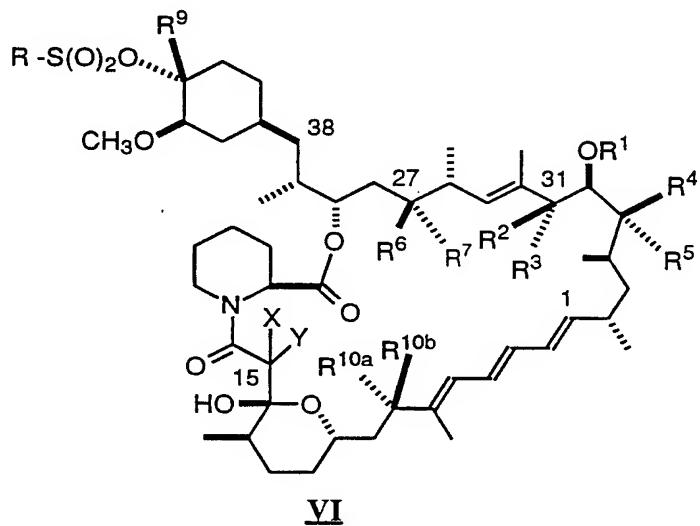
R^{10a} is methoxy and R^{10b} is hydrogen; and

X and Y taken together are oxo.

5

In another aspect of the present invention there are compounds of the formula VI:

10



wherein R is F;

15

R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

20

R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

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R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

- (1) oxo,
- 5 (2) diazo,
- (3) =CH₂,
- (4) -O-(CH₂)₂-O-,
- (5) -S-(CH₂)₂-S-,
- (6) -O-(CH₂)₃-O-,
- 10 (7) -S-(CH₂)₃-S-,
- (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- 15 (9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;

R⁹ is hydrogen;

- 20 R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

- 30 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

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Preferred compounds of the formula VI are those wherein:

- R is F;
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- 5 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ are defined as above;
- R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
- X and Y taken together are oxo.
- 10 More preferred compounds of the formula VI are those wherein:
- R is F;
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- 15 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are
- (1) oxo,
- (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;
- 20 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
- X and Y taken together are oxo.
- 25 Even more preferred compounds of the formula VI are those wherein:

- 30 R is F;
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are

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- (1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

Most preferred compounds of the formula VI are those wherein:

- R is F;
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are oxo;
R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

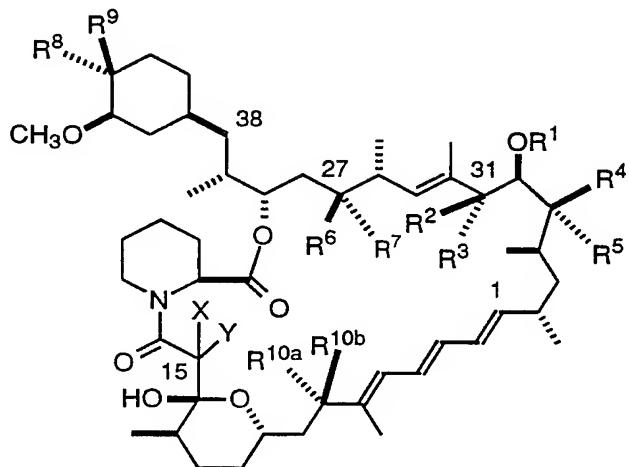
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In another aspect of the present invention there are compounds of the formula VII:



5

VII

wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

10 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

15 R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

- (1) oxo,
- 20 (2) diazo,
- (3) =CH₂,
- (4) -O-(CH₂)₂-O-,
- (5) -S-(CH₂)₂-S-,
- (6) -O-(CH₂)₃-O-,

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(7) -S-(CH₂)₃-S-,

(8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

5

(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;

10 R⁸ is

(1) -O(CH₂)_iC(O)OR²⁰ wherein i is one or two and R²⁰ is independently defined as above,

(2) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are independently selected from

15

- (a) hydrogen,
- (b) loweralkyl,
- (c) alkenyl,
- (d) alkynyl,
- (e) cycloalkyl,

20

(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

25

- (i) hydroxy,
- (ii) -COOH,
- (iii) -CN,
- (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-,

30

- O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,

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- (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
(viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
5 (ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
10 (xii) -SO₃H,
(xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
15 (xvi) oxo and
(xvii) epoxy;
(g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,
20 (k) -NHC(O)-heterocyclic and
(l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
25 (3) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
(4) -O(CH₂)_iC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
30 (5) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
(6) -(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above or
(7) -(CH₂)_iNHC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above;

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R⁹ is hydrogen;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy,
5 alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as
above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy,
alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently
defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is
loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

10 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen
and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

15

Preferred compounds of the formula VII are those wherein:

R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
20 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is defined as above;
R⁹ is hydrogen;
25 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
X and Y taken together are oxo.

More preferred compounds of the formula VII are those wherein:

R¹ is methyl;
30 R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
(1) oxo,

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(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

5 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is

- 10 (1) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are independently selected from
- (a) hydrogen,
 - (b) loweralkyl,
 - (c) alkenyl,
 - (d) alkynyl,
 - 15 (e) cycloalkyl,
 - (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
- 20 (i) hydroxy,
- (ii) -COOH,
 - (iii) -CN,
 - (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,

25 (v) cycloalkyl,

 - (vi) aryl,
 - (vii) heterocyclic,

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- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 5 (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- (xiii) -S(O)₂NH₂,
- (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- 10 (xv) halogen,
- (xvi) oxo and
- (xvii) epoxy;
- (g) aryl,
- (h) heterocyclic,
- 15 (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- (k) -NHC(O)-heterocyclic and
- (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
- 20 or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group or
- (2) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- R⁹ is hydrogen;
- 25 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

Even more preferred compounds of the formula VII are those wherein:

- R¹ is methyl;
- 30 R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are
- (1) oxo,

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- (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
- 5 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclalkyl;
- R⁸ is -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are independently selected from
- 10 (a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,
(e) cycloalkyl,
- 15 (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
- 20 (i) hydroxy,
(ii) -COOH,
(iii) -CN,
(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 25 (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,

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- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 5 (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- (xiii) -S(O)₂NH₂,
- (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- 10 (xv) halogen,
- (xvi) oxo and
- (xvii) epoxy;
- (g) aryl,
- (h) heterocyclic,
- 15 (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- (k) -NHC(O)-heterocyclic and
- (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
- 20 or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- R⁹ is hydrogen;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
- X and Y taken together are oxo.
- 25 Even more preferred compounds of the formula VII are those wherein:
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- 30 R⁶ and R⁷ taken together are
- (1) oxo,
- (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or

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heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

5 R⁸ is -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are independently selected from

- (a) hydrogen,
- (b) loweralkyl,
- (c) alkenyl,
- (d) alkynyl,
- (e) cycloalkyl,

10 (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

- (i) hydroxy,
- (ii) -COOH,
- (iii) -CN,

15 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-,

20 -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,

- (v) cycloalkyl,

- (vi) aryl,

- (vii) heterocyclic,

25 30 (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,

- (ix) guanidino,

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- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- (xiii) -S(O)₂NH₂,
- 5 (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- (xv) halogen,
- (xvi) oxo and
- (xvii) epoxy;
- 10 (g) aryl,
- (h) heterocyclic,
- (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- (k) -NHC(O)-heterocyclic and
- (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is
- 15 carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing
heterocyclic group,
- R⁹ is hydrogen;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
- 20 X and Y taken together are oxo.

Most preferred compounds of the formula VII are those wherein:

- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- 25 R⁴ and R⁵ taken together are oxo;
- R⁶ and R⁷ taken together are oxo;
- R⁸ is -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i is one or two and R²⁴ is hydrogen,
loweralkyl or arylalkyl and R²⁵ is hydrogen, loweralkyl or cycloalkyl;
- R⁹ is hydrogen;
- 30 R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

When examined for immunomodulatory activity using a common *in vitro* biological assay, the compounds of the invention are seen to be potent immunosuppressive agents. The compounds of this invention possess 5 immunosuppressive, antimicrobial, antifungal, antiviral, antiinflammatory and antiproliferative activity. Moreover, the compounds of the invention possess the ability to reverse chemotherapeutic drug resistance. As agents which block T-cell activation, a prerequisite for HIV proliferation, the compounds are useful as prophylactics for the prevention of HIV replication. While, the compounds of 10 the invention are useful when used independently of other agents, combination therapy with other immunosuppressants is beneficial as well. These other immunosuppressant agents include but are not limited to FK-506, rapamycin, cyclosporin A, mycophenolic acid, azathioprine, prednisolone, cyclophosphamide, brequinar and leflunomide.

15 Accordingly, in another aspect of the present invention are disclosed pharmaceutical compositions comprising a compound of the present invention in combination with a pharmaceutically acceptable carrier. Suitable carriers and methods of formulation are also disclosed.

20 In a further aspect of the present invention are disclosed processes for the preparation of the above compounds, synthetic intermediates useful in the preparations of these and other immunomodulatory derivatives of rapamycin.

25 In yet another aspect of the present invention is disclosed a method of immunomodulatory treatment in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of at least one compound of this invention.

Throughout this specification and in the appended claims, the following terms have the meanings specified:

The term "alkanoylamino" as used herein refers to -NHC(O)R¹⁰⁸ wherein 30 R¹⁰⁸ is a loweralkyl group.

The term "alkenyl" as used herein refers to a straight or branched chain radical of 2 to 10 carbon atoms containing at least one carbon-carbon double bond including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-but enyl, 2-but enyl and the like.

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The term "alkenyloxy" as used herein refers to -OR¹⁰⁰ wherein R¹⁰⁰ is an alkenyl group, including but not limited to, 2-propenyl-oxy and the like.

5 The term "alkoxy" as used herein refers to -OR¹⁰¹ wherein R¹⁰¹ is a loweralkyl group including, but not limited to, methoxy, ethoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy and the like.

The term "alkoxyalkoxy" as used herein refers to -OR¹⁰²OR¹⁰³ wherein R¹⁰³ is a loweralkyl group and R¹⁰² is an alkylene group including, but not limited to, methoxymethoxy, ethoxymethoxy and the like.

10 The term "alkoxyalkyl" as used herein refers to an alkyl radical to which is appended an alkoxy group.

The term "alkoxycarbonyl" as used herein refers to -C(O)OR¹⁰⁴ wherein R¹⁰⁴ is a loweralkyl group including, but not limited to, methoxycarbonyl, ethoxycarbonyl and the like.

15 The term "alkoxycarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an aloxycarbonyl group.

The term "alkoxycarbonylthioalkoxy" as used herein refers to -S-R¹⁰⁵-R¹⁰⁶ wherein R¹⁰⁵ is an alkylene group and R¹⁰⁶ is an aloxycarbonyl group.

20 The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-propylene, and the like.

The term "alkylamino" as used herein refers to -NHR¹⁰⁷ wherein R¹⁰⁷ is a loweralkyl group.

25 The term "alkylsulfonylamino" as used herein refers to -NHS(O)₂R¹¹⁰ wherein R¹¹⁰ is a loweralkyl group.

The term "alkynyl" as used herein refers to a straight or branched chain radical of 2 to 10 carbon atoms containing at least one carbon-carbon triple bond including, but not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 30 2-butynyl and the like.

The term "aminocarbonyl" as used herein refers to -C(O)NH₂.

The term "aminocarbonylalkoxy" as used herein refers to -O-R¹⁰⁹-C(O)NH₂ wherein R¹⁰⁹ is an alkylene group.

The term "aryl" as used herein refers to a mono-, bi- or tricyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo, haloalkyl, haloalkoxy, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxycarbonyl, alkoxycarbonylalkenyl, (alkoxycarbonyl)thioalkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aminocarbonyl, aminocarbonylalkoxy, alkanoylamino, arylalkoxy, aryloxy, mercapto, nitro, carboxaldehyde, carboxy, carboxyalkenyl, carboxyalkoxy 5 alkylsulfonylamino, cyanoalkoxy, (heterocyclic)alkoxy, hydroxy, hydroxyalkoxy, phenyl, phenyl-substituted alkenyl, phenyl-substituted alkynyl, heterocyclic, $-S(O)_2NH_2$ and tetrazolylalkoxy. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

10 The term "arylalkoxy" as used herein refers to $-OR^{113}$ wherein R^{113} is an arylalkyl group.

15 The term "arylalkyl" as used herein refers to an alkyl radical to which is appended an aryl group. Examples of arylalkyl include benzyl, 2-phenethyl and the like.

20 The term "aryloxy" as used herein refers to $-OR^{114}$ wherein R^{114} is an aryl group.

The term "bicycloalkenyl" as used herein refers to a bicyclic carbocycle radical containing at least one double bond. Examples of bicycloalkenyl include 1,2-dihydronaphth-4-yl, 1,2,3,4-tetrahydronaphth-1-yl, and the like.

25 The term "carboxyalkenyl" as used herein refers to an alkenyl radical to which is appended a carboxy group.

The term "carboxyalkoxy" as used herein refers to $-OR^{111}$ wherein R^{111} is a carboxyalkyl group.

30 The term "carboxyalkyl" as used herein refers to an alkyl radical to which is appended a carboxy ($-C(O)OH$) group. Examples of carboxyalkyl include carboxymethyl, 2-carboxyethyl and the like.

The term "cyanoalkoxy" as used herein refers to $-O-R^{112}-CN$ wherein R^{112} is an alkylene group.

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The term "cycloalkenyl" as used herein refers to a cycloalkyl group containing at least one double bond. Examples of cycloalkenyl include 1-cyclohexenyl, cyclohex-1-en-3-yl and the like.

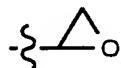
5 The term "cycloalkyl" as used herein refers to a cyclic radical of 3 to 10 carbons including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cycloalkylalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkyl group. Examples of cycloalkylalkyl include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and the like.

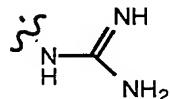
10 The term "dialkylamino" as used herein refers to -NR¹¹⁵R¹¹⁶ wherein R¹¹⁵ and R¹¹⁶ are independently selected from loweralkyl.

The term "diazo" as used herein refers to -N=N-.

The term "epoxy" as used herein refers to



15 The term "guanidino" as used herein refers to



The term "halogen" or "halo" as used herein refers to -Cl, -Br, -F or -I.

20 The term "haloalkoxy" as used herein refers to -OR¹¹⁷ wherein R¹¹⁷ is a haloalkyl group.

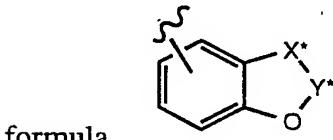
25 The term "haloalkyl" as used herein refers to a loweralkyl radical bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

30 The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; or two sulfur atoms in non-adjacent positions. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The

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nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl,

5 dihydrobenzofuryl or benzothienyl and the like). Heterocyclics include: azetidinyl, oxetanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, 10 thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrimidyl and benzothienyl. Heterocyclics also include compounds of the



formula where X^* is $-CH_2-$ or $-O-$ and Y^* is $-C(O)-$ or $[-C(R'')_2]_v$ where R'' is hydrogen or C_1-C_4 -alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

Heterocyclics also include bicyclic spirocyclic heterocycles such as the ethylene ketal of pyridin-2-on-1-yl, the ethylene ketal of pyridin-4-on-1-yl and the like.

20 Heterocyclics also include hexose monosaccharides (for example, D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose and the like) and pentose monosaccharides (for example, D-ribose, D-arabinose, D-xylose, D-lyxose and the like).

25 Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo ($=O$), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, alkoxyalkyl, haloalkyl, hydroxy, hydroxyalkyl, cycloalkyl, aryl, arylalkyl, $-COOH$, $-SO_3H$, $-C(O)NH_2$ and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

30 The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above.

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The term "heterocyclicalkoxy" as used herein refers to -OR¹¹⁸ wherein R¹¹⁸ is a heterocyclicalkyl group.

The term "hydroxyalkyl" as used herein refers to an alkyl radical to which is appended an hydroxy group. Examples of hydroxyalkyl include 5 hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl and the like.

The term "hydroxyalkoxy" as used herein refers to -O-R¹¹⁹-OH wherein R¹¹⁹ is an alkylene group.

The term "hydroxy protecting group" as used herein refers to those radicals which are known in the art of organic synthesis to protect a hydroxyl 10 group against undesirable reaction during synthetic procedures and to be selectively removable such as those hydroxy protecting groups disclosed in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Son, Inc., 1991, which is hereby incorporated herein by reference.

Examples include, but are not limited to, substituted methyl ethers, for example, 15 methoxymethyl, methylthiomethyl, 2-methoxyethoxymethyl, benzyloxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichoroethyl; silyl ethers, for example, dimethylhexylsilyl, trisubstituted silyl such as tris(loweralkyl)silyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tri-20 isopropylsilyl, *tert*-butyldimethylsilyl, tri-*tert*-butylsilyl, triphenylsilyl, triphenylmethyldimethylsilyl, etc.), loweralkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, *tert*-butyldiphenylsilyl, etc.), triarylsilyl (e.g., triphenylsilyl, trixylylsilyl, etc.) and triarylalkylsilyl (e.g., tribenzylsilyl, etc.); -C(O)H; -C(O)-loweralkyl (for 25 example, acetyl, propionyl, pivaloyl, t-butylacetyl and the like); -C(O)-aryl (for example, benzoyl and the like); alkoxy carbonyl (for example, ethoxycarbonyl and the like); -S(O)₂-(loweralkyl); -S(O)₂-(aryl); and the like.

The term "loweralkyl" as used herein refers to a monovalent straight chain or branched chain radical of 1 to 10 carbon atoms including, but not 30 limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, decyl and the like.

The term "oxo" as used herein refers to (=O).

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The term "tetrazolylalkoxy" as used herein refers to -O-R¹²⁰-tetrazolyl wherein R¹²⁰ is an alkylene group.

The term "pharmaceutically acceptable salts, esters, amides and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. (See, for example S. M. Berge et al., "Pharmaceutical Salts," J. Pharm. Sci., **66**: 1-19 (1977) which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C₁-C₆ alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C₅-C₇ cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C₁-C₄ alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

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Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C1-C6 alkyl amines and secondary C1-C6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may 5 also be in the form of a 5 or 6 membered heterocycle containing one secondary nitrogen atom. Amides derived from ammonia, C1-C3 alkyl primary amides and di(C1-C2 alkyl) secondary amides are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which 10 15 are incorporated herein by reference.

Where appropriate, prodrugs of derivatives of compounds of the present invention may be prepared by any suitable method. For those compounds in which the prodrug moiety is an amino acid or peptide functionality, the condensation of the amino group with amino acids and peptides may be effected 20 in accordance with conventional condensation methods such as the azide method, the mixed acid anhydride method, the DCC (dicyclohexylcarbodiimide) method, the active ester method (p-nitrophenyl ester method, N-hydroxysuccinic acid imide ester method, cyanomethyl ester method and the like), the Woodward reagent K method, the DCC-HOBT (1-hydroxy-benzotriazole) method and the 25 like. Classical methods for amino acid condensation reactions are described in "Peptide Synthesis" Second Edition, M. Bodansky, Y.S. Klausner and M.A. Ondetti (1976).

As in conventional peptide synthesis, branched chain amino and carboxyl groups at alpha and omega positions in amino acids may be protected and 30 deprotected if necessary. The protecting groups for amino groups which can be used involve, for example, benzyloxycarbonyl (Cbz), o-chlorobenzyloxycarbonyl ((2-Cl)Cbz)), p-nitrobenzyloxycarbonyl (Cbz(NO₂)), p-methoxybenzyloxycarbonyl(Cbz(OMe)), t-amyoloxycarbonyl (Aoc), isobornealoxycarbonyl, adamantyloxycarbonyl (Adoc), 2-(4-biphenyl)-2-

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propyloxy carbonyl (Bpoc), 9-fluorenyl-methoxycarbonyl (Fmoc), methylsulfonylethoxy carbonyl (Msc), trifluoroacetyl, phthalyl, formyl, 2-nitrophenylsulfonyl (Nps), diphenylphosphinothioyl (Ppt) and dimethylphosphino-thioyl (Mpt).

5 Examples of protecting groups for carboxyl groups include, for example, benzyl ester (OBzl), cyclohexyl ester, 4-nitrobenzyl ester (OBzlNO₂), t-butyl ester (OtBu), 4-pyridylmethyl ester (OPic) and the like.

In the course of the synthesis of certain of the compounds of the present invention, specific amino acids having functional groups other than amino and 10 carboxyl groups in the branched chain such as arginine, cysteine, serine and the like may be protected, if necessary, with suitable protecting groups. It is preferable that, for example, the guanidino group (NG) in arginine may be 15 protected with nitro, p-toluenesulfonyl (Tos), benzyloxycarbonyl (Z), adamantlyloxycarbonyl (Adoc), p-methoxybenzenesulfonyl, 4-methoxy-2,6-dimethyl-benzenesulfonyl (Mts) and the like; the thiol group in cysteine may be 20 protected with benzyl, p-methoxybenzyl, triphenylmethyl, acetamidomethyl, ethylcarbamyl, 4-methylbenzyl (4-MeBzl), 2,4,6-trimethylbenzyl (Tmb) and the like; and the hydroxy group in serine may be protected with benzyl (Bzl), t-butyl, acetyl, tetrahydropyranyl (THP) and the like.

20 The term "protected hydroxy" as used herein refers to the oxygen atom of a hydroxy radical to which has been appended a "hydroxy protecting group" as defined above.

The compounds of the invention may be prepared using one or more of 25 the processes which follow. The starting materials for use in these processes are preferably one of the macrolides isolated from culture media obtained in accordance with known methods by fermentation of *Streptomyces hydroscopicus*, which are disclosed in U.S. Patent Nos. 3,929,992 and 3,993, 749; *Journal of Antibiotics* 1975, 28 (10), 721-726, 727-732 and *Journal of Antibiotics* 1978, 31 (6), 539-545. One or more of the processes discussed below 30 may be then employed to produce the desired compound of the invention.

Such processes comprise:

(a) producing by selective activation a compound of formula I or VI comprising reacting a corresponding precursor in which one of R⁸ and R⁹ is

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hydrogen and the other is hydroxy with an appropriate amount of fluorosulfonyl anhydride under conditions suitable for the production of the desired product;

(b) producing by selective activation a compound of formula I or VI comprising reacting a corresponding precursor in which one of R⁸ and R⁹ is

5 hydrogen and the other is hydroxy with an appropriate amount of trifluoromethanesulfonyl anhydride under conditions suitable for the production of the desired product;

(c) producing a compound of formula I in wherein R⁸ is hydrogen and R⁹ is -OC(=O)-O-aryl, -OC(=O)-O-(N-succinimidyl), -OC(=O)-triazole,

10 -OC(=O)-imidazolyl, or -OC(=O)-O-benzotriazolyl by reacting a corresponding precursor in which R⁸ is hydrogen and R⁹ is hydroxy with appropriate chloroformates or activated carbonyl compounds;

(d) producing a compound of formula I wherein R⁸ is hydrogen and R⁹ is -OC(=O)-NR²⁴R²⁵ by reacting a corresponding precursor in which R⁸

15 is hydrogen and R⁹ is -OC(=O)-O-aryl, -OC(=O)-O-(N-succinimidyl), -OC(=O)-triazolyl, -OC(=O)-imidazolyl, or -OC(=O)-(hydroxybenzotriazolyl) with appropriate amines (HNR²⁴R²⁵);

(e) producing a compound of formula I in which R⁸ is hydrogen and R⁹ is hydroxy by reacting a corresponding precursor in which R⁹ is hydrogen and R⁸ is -OS(O)₂F or -O-S(O)₂CF₃ with water in an appropriate solvent;

(f) producing a compound of formula I in which R⁸ is hydrogen and R⁹ is -O-formyl by reacting a corresponding precursor in which R⁹ is hydrogen and R⁸ is -OS(O)₂F or -OS(O)₂CF₃ with N,N-dimethylformamide and water;

(g) producing a compound of formula II or III in which R⁸ is hydrogen and R⁹ is -SR²⁴ or -NR²⁴R²⁵ by reacting a corresponding precursor in which R⁹ is hydrogen and R⁸ is -OS(O)₂F or -OS(O)₂CF₃ with H-SR²⁴, H₂NC(S)NH₂, or H-NR²⁴R²⁵;

(h) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)OR²⁰, where R²⁰ is as defined above, by etherification of the corresponding hydroxy compound;

(i) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)NR²⁴R²⁵, where NR²⁴R²⁵ is as defined above, by etherification of the corresponding hydroxy compound;

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- (j) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)N(OR²⁴)R²⁵, where R²⁴ and R²⁵ are as defined above, by etherification of the corresponding hydroxy compound;
- 5 (k) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)NR²⁴NR²⁴R²⁵, where R²⁴ and R²⁵ are as defined above, by etherification of the corresponding hydroxy compound;
- (l) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)R²⁴, where R²⁴ is as defined above, by etherification of the corresponding hydroxy compound;
- 10 (m) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)NR²⁴R²⁵, wherein -NR²⁴R²⁵ is as defined above, by etherification of the corresponding hydroxy compound;
- (n) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)N(OR²⁴)(R²⁵), wherein -NR²⁴R²⁵ is as defined above, by etherification of the corresponding hydroxy compound;
- 15 (o) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)NR²⁴NR²⁴R²⁵, wherein -NR²⁴R²⁵ is as defined above, by etherification of the corresponding hydroxy compound;
- (p) producing a compound of formula I or VII in which one of R⁸ and R⁹ is -OCH₂-NHC(O)R²⁴ and the other is hydrogen by (i) activating a corresponding -OCH₂C(O)OH functionality, (ii) generating therefrom, directly or in a subsequent synthetic step, a -OCH₂C(O)N₃ functionality, (iii) performing a Curtius rearrangement, (iv) trapping with a carboxylic acid having the formula R²⁴CO₂H, and (v) heating to generate the desired -OCH₂-NHC(O)R²⁴ moiety;
- 20 (q) and
- (r) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)NR²⁴R²⁵, wherein -NR²⁴R²⁵ is as defined above, by formation of a -OCH₂-N=C=O isocyanate group followed by addition of an amine HNR¹⁴R¹⁵;
- 25 (s) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)NR²⁴R²⁵, where R²⁴ and R²⁵ are as defined above, by condensation of NHR²⁴R²⁵ with a -OCH₂C(O)OR²⁰ group in a corresponding compound;

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- (s) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)N(OR²⁴)R²⁵, where R²⁴ and R²⁵ are as defined above, by condensation of NH(OR²⁴)R²⁵ with a -OCH₂C(O)OR²⁰ group in a corresponding compound;
- 5 (t) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂C(O)NR²⁴NR²⁴R²⁵, where R²⁴ and R²⁵ are as defined above, by condensation of NHR²⁴NR²⁴R²⁵ with a -OCH₂C(O)OR²⁰ group in a corresponding compound;
- 10 (u) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)N(OR²⁴)R²⁵, wherein R²⁴ and R²⁵ are as defined above, by formation of a -OCH₂-N=C=O isocyanate group followed by addition of HN(OR²⁴)R²⁵;
- 15 (v) producing a compound of formula I or VII in which one of R⁸ and R⁹ is hydrogen and the other is -OCH₂-NHC(O)NR²⁴NR²⁴R²⁵, wherein -NR²⁴R²⁵ and R²⁴ are as defined above, by formation of a -OCH₂-N=C=O isocyanate group followed by addition of HNR²⁴NR²⁴R²⁵;
- 20 (w) producing a compound of formula I, wherein R⁹ is -N₃, by displacement of an -OS(O)₂F or -OS(O)₂CF₃ group in a corresponding compound;
- (x) producing a compound of formula III, wherein R⁹ is -NH₂, by reduction of the -N₃ group in a corresponding compound;
- 25 (y) producing a compound of formula III, wherein R⁹ is -NHCOR*, by acylation of the corresponding amine;
- (z) producing a compound of formula III, wherein R⁹ is -NHC(O)NR^aR^b, by acylation of the corresponding amine;
- (aa) producing a compound of formula III, wherein R⁹ is a -NH-SO₂R* group, by selective sulfonylation of the corresponding amine;
- (bb) producing a compound of formula III, wherein R⁹ is -NH-C(=O)OR group, by acylation of the corresponding amine;
- 30 (cc) producing a compound of formula III, wherein R⁹ is -NH-SR*, by sulfenylation of the corresponding amine;
- (dd) producing a compound of formula III, wherein R⁹ is -N=C=O, by isocynate formation from the corresponding amine;

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- (ee) producing a compound of formula III, wherein R⁹ is -Se-Ph, by displacement of a corresponding -OS(O)₂F or -OS(O)₂CF₃ group;
- (ff) producing a compound of formula II, wherein R⁹ is -Se(O)-Ph, by oxidation of a corresponding -SePh group;
- 5 (gg) producing a compound of formula IV, where one of R⁸ and R⁹ with one of R¹⁸ and R¹⁹ taken together form a bond, the others of R⁸, R⁹, R¹⁸ and R¹⁹ are hydrogen, by selective 1,2-elimination of an H-OSePh group in a corresponding compound containing an -Se(O)Ph group;
- 10 (hh) producing a compound of formula IV, where one of R⁸ and R⁹ is OH and one of R¹⁸ and R¹⁹ is OH, and the others of R⁸, R⁹, R¹⁸ and R¹⁹ are hydrogen by selective 1,2-dihydroxylation of an olefin of a corresponding compound;
- 15 (ii) producing a compound of formula IV, where R⁸ or R⁹ and R¹⁸ or R¹⁹ taken together form a -OC(=O)O-, -OS(=O)O-, -OS(O)2-, -O(CH₂)O- or -CO(CH₂)_mCO-, where m=0 to 6, and the others of R⁸, R⁹, R¹⁸ and R¹⁹ are hydrogen by selective functionalization of a 1,2-dihydroxy group of a corresponding compound;
- 20 (jj) producing a compound of formula I-VII, where R^{10a} = R^{10b} = H from a corresponding compound;
- (kk) producing a compound of formula I-VII, where R^{10a} = H, R^{10b} = OCH₃, or R^{10a} = allyl, R^{10b} = H from a corresponding compound;
- 25 (ll) producing a compound of formula IVc where R⁸ and R⁹ taken together are oxo, by reacting a compound of formula I wherein R⁸ is hydrogen and R⁹ is -OH or R⁸ is OH and R⁹ is hydrogen with fluorosulfonyl anhydride or trifluoromethylsulfonyl anhydride, followed by reaction of the resulting sulfonate with silica gel or an appropriate base to produce the enol ether, followed by hydrolysis of the enol ether; or
- (mm) producing a compound of formula IVd by rearrangement of a compound of formula I where R⁸ is -OSO₂F or -OSO₂CF₃ and R⁹ is hydrogen, in the presence of silica gel or appropriate mild acid under conditions suitable for the production of the desired product and hydrolysis of the enol ether.

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In process (a), a suitable reagent for activation of an alcohol is fluorosulfonyl anhydride (prepared according to the procedure described by S. Kongpricha, W.G. Preusse and R. Schwarer, in Inorganic Synthesis, 1968, 11, pp. 151-155). The activation may be carried out in a solvent which does not 5 adversely affect the reaction (e.g. diethyl ether, dichloromethane, tetrahydrofuran, chloroform or N-methylpyrrolidone or a mixture thereof). The reaction may require cooling or heating, depending on the method used. Further, the reaction is preferably conducted in the presence of an organic or inorganic base such as cesium bicarbonate, pyridine, lutidine, picoline, quinoline, 10 diisopropylethylamine and the like. The reaction temperature is preferably from -100 to 30 °C, and more preferably from -78 to 0 °C. The reaction may require 20 minutes to 24 hours to complete, depending on the reagent chosen.

In process (b), a suitable reagent for activation of an alcohol is trifluoromethanesulfonyl anhydride (Aldrich). The activation may be carried out 15 in a solvent which does not adversely affect the reaction (e.g. diethyl ether, dichloromethane, tetrahydrofuran, chloroform or N-methylpyrrolidone or a mixture thereof). The reaction may require cooling or heating, depending on the method used. Further, the reaction is preferably conducted in the presence of an organic or inorganic base such as cesium bicarbonate, pyridine, lutidine, picoline, quinoline, diisopropylethylamine and the like. The reaction 20 temperature is preferably from -100 to 30 °C, and more preferably from -78 to 0 °C. The reaction may require 20 minutes to 24 hours to complete, depending on the reagent chosen.

In process (c), a suitable reagent for the formation of an activated alcohol 25 derivative is an aryl chlorofomate, heterocyclic chloroformate, 1,1'-carbonyldiimidazole, di-(N-succinimidyl)carbonate, or carbonyldi-(hydroxybenzotriazole). The activation may be carried out in a solvent which does not adversely affect the reaction (e.g. diethyl ether, dichloromethane, tetrahydrofuran, chloroform or N-methylpyrrolidone, pyridine or a mixture 30 thereof). The reaction may require cooling or heating, depending on the method used. Further, the reaction is preferably conducted in the presence of an organic or inorganic base such as cesium bicarbonate, pyridine, lutidine, picoline, quinoline, diisopropylethylamine and the like. The reaction temperature is

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preferably from 0 °C to 100 °C. The reaction may require 20 minutes to 24 hours to complete, depending on the reagent chosen.

In process (d), a suitable reagent for the formation of a carbamate is any suitable amine. The reaction may be carried out in a solvent which does not 5 adversely affect the reaction (e.g. diethyl ether, dichloromethane, tetrahydrofuran, chloroform or N-methylpyrrolidone, pyridine or a mixture thereof). The reaction may require cooling or heating, depending on the method used. Further, the reaction is preferably conducted in the presence of an organic or inorganic base such as cesium bicarbonate, pyridine, lutidine, picoline, 10 quinoline, diisopropylethylamine and the like. The reaction temperature is preferably from 0 °C to 100 °C. The reaction may require 20 minutes to 24 hours to complete, depending on the reagent chosen.

In process (e), a suitable reagent for inversion is water. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. 15 dioxane, DMSO, acetonitrile, tetrahydrofuran, or N-methylpyrrolidone, pyridine or a mixture thereof). The reaction may require cooling or heating, depending on the method used. The reaction temperature is preferably from 0 °C to 100 °C. The reaction may require 20 minutes to 24 hours to complete, depending on the solvent chosen.

20 In process (f), a suitable reagent and solvent for inversion is N,N-dimethylformamide. The reaction temperature is preferably from 0 °C to 100 °C. The reaction may require 20 minutes to 24 hours to complete.

In process (g), suitable reagents are H-SR²¹, H-NR²⁴R²⁵, or 25 H₂NC(S)NH₂ and a secondary- or tert-amine base such as morpholine or Hunig's base. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. methylene chloride, dioxane, acetonitrile, tetrahydrofuran, N,N,N,N,-tetraalkylurea, or N-methylpyrrolidone, pyridine or a mixture thereof). The reaction temperature is preferably from 0 °C to 100 °C. The reaction may require 20 minutes to 24 hours to complete.

30 In processes (h), (i), (j), (k), (l), (m), (n) and (o), ether formation may be carried out using, for example, appropriately substituted alkyl halides in the presence of KY-zeolite (Onaka, M.; Kawai, M.; Izumi, Y. *Chem. Lett.* 1983, 1101), polymeric materials (Kimura, Y.; Kirszensztein, P.; Regen, S. L. *J. Org. Chem.* 1983, 48, 385), nickel-catalysis (Camps, F.; Coll, J.; Moreto, J. M.

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Synthesis 1982, 186; Yamashita. *Synthesis* 1977, 803), arylalkyl-*O*-p-toluenesulfonate (Dewick, P. M. *Synth. Commun.* 1981, 11, 853), potassium or sodium alkoxides (Bates, R. B.; Janda, K. D. *J. Org. Chem.* 1982, 47, 4374), pyridine or other bases (*Chem. Lett.* 1978, 57), tetraalkylammonium halide (Miller, J. M.; So, K. H.; Clark, J. H. *Can. J. Chem.* 1979, 1887), mercury perchlorate (McKillop, A.; Ford, M. E. *Tetrahedron* 1974, 30, 2467), silver triflate or silver oxide (Kuhn, R.; Löw, I.; Trischmann, H. *Chem. Ber.* 1957, 90, 203. Croon, I.; Lindberg, B. *Acta Chem. Scand.*, 1959, 13, 593) or a phase transfer catalyst (McKillop, A.; Fiaud, J.-C.; Hug, R. P. *Tetrahedron* 1974, 30, 1379). The ether formation may also be carried out with dialkyl- or diarylphosphoric acid in the presence of p-toluenesulfonic acid (Kashman, Y. *J. Org. Chem.* 1972, 37, 912), with diazo compounds with tin(II) chloride (Christensen, L. F.; Broom, A. D. *J. Org. Chem.* 1972, 37, 3398), or with 2,2,2-trichloroalkanols in the presence of base (Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* 1992, 114, 1906; Corey, E. J.; Link, J. O. *Tetrahedron Lett.* 1992, 33, 3431). Additionally, ether formation may be accomplished with a suitable trichloroacetimidate in the presence of an acid catalyst (Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc. Perk Trans.* 1985, 1, 2247.) The ether formation may be carried out in a solvent which does not adversely affect the reaction (e.g. acetone, dichloromethane, tetrahydrofuran, pyridine, *N,N*-dimethylformamide, ether, acetonitrile, cyclohexane, etc. or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

O-Alkylation may be carried out using substituted alkyl halides, substituted alkyl trifluoromethanesulfonates, substituted fluorosulfonates, and the like in the presence of an appropriate base such as triethylamine, potassium fluoride, silver carbonate, silver triflate or silver(I) oxide. The reaction is performed in an inert solvent such as *N,N*-dimethylformamide, acetonitrile or dichloromethane, preferably between -78 °C and 80 °C. Alternatively, alkylation can be carried out using substituted diazoalkanes, such as diazomethane, ethyl diazoacetate, and the like, in the presence of a metal catalyst, for example Rh(OAc)₂ in an inert solvent such as dichloromethane preferably between -20 °C and 80 °C.

In process (p), -OCH₂-NHC(O)R²⁴ formation may be carried out by first forming an -O-CH₂-C(O)N₃ by activating a -O-CH₂-C(O)OH in the molecule

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with a chloroformate, such as isobutyl chloroformate, in the presence of a tertiary amine, such as N-methyl-morpholine or N-methyl-piperidine, and treating with an azide source, such as sodium azide, hydrazoic acid, trimethylsilylazide, or tetramethylguanidinium azide. The acyl azide may also be formed directly using diphenylphosphorylazide in the presence of a tertiary amine. The reaction mixture is then heated at from 40 °C to 100 °C for 0.5 to 6 hours, whereupon R²⁴CO₂H is added and the reaction is heated between 40 °C and 120 °C in a inert solvent to form -OCH₂-NHC(O)R²⁴.

In process (q), the -O-CH₂-NHC(O)NR²⁴R²⁵ formation may be carried out by first forming an -O-CH₂-C(O)N₃ by activating a -O-CH₂-C(O)OH in the molecule with a chloroformate, such as isobutyl chloroformate, in the presence of a tertiary amine, such as N-methyl-morpholine or N-methyl-piperidine, and treating with an azide source, such as sodium azide, hydrazoic acid, trimethylsilylazide, or tetramethylguanidinium azide. The acyl azide may also be formed directly using diphenylphosphorylazide in the presence of a tertiary amine. The reaction mixture is then heated at from 40 °C to 100 °C for 0.5 to 6 hours, whereupon the amine HNR²⁴R²⁵ is added at a temperature at from 23 °C to 100 °C. The reaction is conducted in an inert organic solvent such as diethyl ether, tetrahydrofuran, 1,4-dioxane, chloroform, methylene chloride, benzene or toluene; alternatively the -O-CH₂-NHC(O)NR²⁴R²⁵ moiety may be formed by alkylation of the C42 hydroxyl group with LG-CH₂-NHC(O)NR²⁴R²⁵, where LG may be halogen or activated hydroxyl, such as mesylate, triflate, fluorosulfonate and the like.

In process (r) condensation of an amine with a group of formula -O-(CH₂)_iC(O)OH, may be performed using the mixed or symmetrical anhydride of said acid, the acyl cyanide of the carboxylic acid, or acyl azide of the carboxylic acid. Alternatively, in a group of formula -O-(CH₂)_iC(O)OR^{20a}, where R^{20a} is defined as R²⁰ excluding hydrogen, OR^{20a} is displaced by NR²⁴R²⁵, where the exchange is conducted in an inert solvent, such as dichloromethane, and may be facilitated by Al(CH₃)₃, Sn[N(Si(CH₃)₃)₂]₂, a Grignard reagent and the like.

In process (s) condensation of NH(OR²⁴)R²⁵, where R²⁴ and R²⁵ are as defined above, with a group of formula -O-(CH₂)_iC(O)OH, may be performed using the mixed or symmetrical anhydride of said acid, the acyl cyanide of the

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carboxylic acid, or acyl azide of the carboxylic acid. Alternatively, in a group of formula -O-(CH₂)_iC(O)OR^{20a}, where R^{20a} is defined as R²⁰ excluding hydrogen, OR^{20a} is displaced by N(OR²⁴)R²⁵, where the exchange is conducted in an inert solvent, such as dichloromethane, and may be facilitated by Al(CH₃)₃, 5 Sn[N(Si(CH₃)₃)₂]₂, a Grignard reagent and the like.

In process (t) condensation of NHR²⁴NR²⁴R²⁵, where R²⁴ and R²⁵ are as defined above, with a group of formula -O-(CH₂)_iC(O)OH, may be performed using the mixed or symmetrical anhydride of said acid, the acyl cyanide of the carboxylic acid, or acyl azide of the carboxylic acid. Alternatively, in a group of 10 formula -O-(CH₂)_iC(O)OR^{20a}, where R^{20a} is defined as R²⁰ excluding hydrogen, OR^{20a} is displaced by NR²⁴NR²⁴R²⁵, where the exchange is conducted in an inert solvent, such as dichloromethane, and may be facilitated by Al(CH₃)₃, Sn[N(Si(CH₃)₃)₂]₂, a Grignard reagent and the like.

In process (u), the -O-CH₂-NHC(O)N(OR²⁴)R²⁵ formation may be 15 carried out by first forming an -O-CH₂-C(O)N₃ by activating a -O-CH₂-C(O)OH in the molecule with a chloroformate, such as isobutyl chloroformate, in the presence of a tertiary amine, such as N-methyl-morpholine or N-methyl-piperidine, and treating with an azide source, such as sodium azide, hydrazoic acid, trimethylsilylazide, or tetramethylguanidinium azide. The acyl azide may 20 also be formed directly using diphenylphosphorylazide in the presence of a tertiary amine. The reaction mixture is then heated at from 40 °C to 100 °C for 0.5 to 6 hours, whereupon the amine HN(OR²⁴)R²⁵ is added at a temperature at from 23 °C to 100 °C. The reaction is conducted in an inert organic solvent such as diethyl ether, tetrahydrofuran, 1,4-dioxane, chloroform, methylene chloride, 25 benzene or toluene; alternatively the -O-CH₂-NHC(O)N(OR²⁴)R²⁵ moiety may be formed by alkylation of the C42 hydroxyl group with LG-CH₂-NHC(O)N(OR²⁴)R²⁵, where LG may be halogen or activated hydroxyl, such as mesylate, triflate, fluorosulfonate and the like.

In process (v), the -O-CH₂-NHC(O)NR²⁴NR²⁴R²⁵ formation may be 30 carried out by first forming an -O-CH₂-C(O)N₃ by activating a -O-CH₂-C(O)OH in the molecule with a chloroformate, such as isobutyl chloroformate, in the presence of a tertiary amine, such as N-methyl-morpholine or N-methyl-piperidine, and treating with an azide source, such as sodium azide, hydrazoic

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acid, trimethylsilylazide, or tetramethylguanidinium azide. The acyl azide may also be formed directly using diphenylphosphorylazide in the presence of a tertiary amine. The reaction mixture is then heated at from 40 °C to 100 °C for 0.5 to 6 hours, whereupon the amine HNR²⁴NR²⁴R²⁵ is added at a temperature 5 at from 23 °C to 100 °C. The reaction is conducted in an inert organic solvent such as diethyl ether, tetrahydrofuran, 1,4-dioxane, chloroform, methylene chloride, benzene or toluene; alternatively the -O-CH₂-NHC(O)NR²⁴NR²⁴R²⁵ moiety may be formed by alkylation of the C42 hydroxyl group with LG-CH₂-NHC(O)NR²⁴NR²⁴R²⁵, where LG may be halogen or activated hydroxyl, 10 such as mesylate, triflate, fluorosulfonate and the like.

In process (w), suitable azide reagents include well-established alkali metal azides such as sodium or lithium azides (NaN₃ or LiN₃) in the presence or absence of crown ethers, more reactive tetraalkylammonium azides (Danishefski, S. J.; DeNinno, M. P.; Chen, S.-H. *J. Am. Chem. Soc.* **1988**, *110*, 3929), a 15 copper-assisted azide reaction (Yamamoto, Y.; Asao, N. *J. Org. Chem.* **1990**, *55*, 5303) and a hydrogen azide-amine system (Saito, S.; Yokoyama, H.; Ishikawa, T.; Niwa, N.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 663; Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 667). The azide displacement reaction may be carried out in a solvent which does not 20 adversely affect the reaction (e.g. chloroform, acetone dichloromethane, tetrahydrofuran, pyridine, dimethylsulfoxide, *N,N*-dimethylformamide, hexamethylphosphoramide, etc. or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (x), the reduction may be carried out catalytically using 25 hydrogen. Suitable catalysts include, but are not limited to platinum catalysts (e.g. platinum oxide, platinum black), palladium catalysts (e.g. palladium oxide, palladium on charcoal, palladium black, palladium hydroxide on charcoal, palladium on calcium carbonate poisoned with lead, palladium on barium carbonate with quinoline), nickel catalysts (e.g. nickel oxide, Raney nickel), 30 rhodium catalysts (e.g. rhodium on alumina). Reduction may also be carried out using metal reducing reagents (see Review; Scriven, E. F. V.; Turnbull, K. *Chem Rev.* **1988**, *88*, 321; Patai, S., Ed., "The Chemistry of the Azido Group," Interscience Publishers, New York, **1971**; Scriven, E. F. V., Ed., "Azides and

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Nitrenes Reactivity and Utility," Academic Press, Inc., New York, 1984) such as sodium borohydride under phase-transfer conditions, borohydride supported on an ion exchange resin, lithium aluminum hydride and the like, furthermore, 1,3-propanedithiol-triethylamine method (Bayley, H.; Staudring, D. N.; Knowles, J. R. *Tetrahedron Lett.* 1978, 3633), triphenylphosphine (Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* 1983, 24, 763), and sodium tellurium hydride (Suzuki, H.; Takaoka, K. *Chem Lett.* 1984, 1733).

The reduction may be carried out in a solvent which does not adversely affect the reaction (e.g., alcohols, water, acetone, dichloromethane, tetrahydrofuran, pyridine or *N,N*-dimethylformamide or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (y), suitable *N*-acylations may be carried out using the methods of symmetric carboxylic acid anhydrides, carboxylic acid halides, mixed carbonic-carboxylic anhydrides, active esters (*p*-nitrophenylester, trichlorophenyl ester, pentafluorophenyl ester, *N*-hydroxysuccinimide, cyanoethyl and the like), and carboxylic acid with suitable condensing reagents such as DCC (*N,N*-dicyclohexylcarbodiimide and its related condensing agents), DCC-HOBt (*N,N*-dicyclohexylcarbodiimide-1-hydroxybenzotriazole), Woodward reagent K method, *N,N*-carbonyldiimidazole and phosphonium containing reagents (e.g. benzotriazolyloxytris[dimethylamino]phosphonium hexafluorophosphate, *N,N*-bis[2-oxo-3-ox-azolidinyl]phosphorodiamidic chloride, diethylphosphorobromide, diphenylphosphoryl azide, bromo tris[dimethylamino]phosphonium hexafluorophosphate, and the like). Suitable reagents for amide formation include, but are not limited to formyl derivatives, acetyl halides (chloroacetyl, trichloroacetyl, *o*-nitrophenylacetyl, *o*-nitrophenoxyacetyl, acetoacetyl, [*N*'-dithiobenzoyloxycarbonylamino]acetyl and the like), and substituted propionyl derivatives (3-phenylpropionyl, isobutyryl, picolinoyl, and the like). Other groups may be found in volume 3 of *The Peptides* Gross, E. and Meinhofer, J. Academic Press, 1981 and *Protective Groups in Organic Synthesis* Greene, T. W. John Wiley & Sons, New York, Chapter 7, 1981. Typically used coupling conditions are described by Gross, E.; Meinhofer, J. "The Peptides" vol. 3, Academic Press, 1981. The *N*-acylation may be carried out in a solvent which does not adversely affect the reaction (e.g. acetone, dichloromethane, chloroform, tetrahydrofuran, *N,N*-dimethylformamide,

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dimethylsulfoxide, diethylether, and the like, or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (z), urea formation may be carried out from the following reactions; reaction with silicon tetraisocyanate or silicon tetraiso thiocyanate (Neville, R. G.; McGee, J. J. *Can. J. Chem.* **1963**, *41*, 2123), reaction with *N,N*-carbonyldiimidazole or *N,N*-thiocarbonyldiimidazole, followed by *N*-substituted primary or secondary amines or ammonia (Staab, H. A.; Wendel, K. *Org. Synth.* **1968**, *48*, 44), and reaction with phosgene or thiophosgene in the presence of *tert*-amine, followed by *N*-substituted primary or secondary amines or ammonia.

The ureido formation may be carried out in a solvent which does not adversely affect the reaction (e.g. acetone, toluene, dichloromethane, tetrahydrofuran, pyridine, *N,N*-dimethylformamide, etc. or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (aa), *N*-sulfonylation may be carried out using substituted sulfonylhalides in the presence of suitable *tert*-amines such as trialkylamine, pyridine, and the like (Remers, W. A.; Roth, R. H.; Gibbs, G. J.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 1232). Suitable reagents include, but are not limited to benzenesulfonyl halide, *p*-methoxybenzenesulfonyl halide, 2,4,6-trimethylbenzenesulfonyl halide, toluenesulfonyl halide, benzylsulfonyl halide, *p*-methoxybenzylsulfonyl halide, trifluoromethylsulfonyl halide, phenacylsulfonyl halide, and the like. Some other representative groups may be found in volume 3 of *The Peptides*, Gross, E. and Meinhofer, J. Academic Press, **1981** and *Protective Groups in Organic Synthesis*, Greene, T. W. John Wiley & Sons, New York, Chapter 7, **1981**. The *N*-aryl- or alkylsulfonylation may be carried out in a solvent which does not adversely affect the reaction (e.g., acetone, dichloromethane, tetrahydrofuran, pyridine or *N,N*-dimethylformamide or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (bb), *N*-carbamate formations may be carried out using common protecting groups for amino group such as, but not limited to methylcarbamates (cyclopropylmethyl, 9-fluorenylmethyl, and the like), substituted ethylcarbamates (2,2,2-trichloroethyl, 2-phosphonoethyl, 2-methylthioethyl, and the like), substituted propyl and isopropylcarbamates (1,1-dimethylpropynyl, 1-methyl-1-(4-biphenylyl)ethyl, *tert*-butyl, phenyl, *p*-

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nitrobenzyl, 8-quinolyl, *N*-hydroxypiperidinyl, benzyl, dimethoxybenzyl, 9-anthrylmethyl, 1-adamantyl, cyclohexyl, *tert*-amyl, cinnamoyl, isobutyl, *N'*-*p*-phenylaminothiocarbonyl, *N'*-piperidinylcarbonyl, diphenylmethyl, and the like). Preparations of *N*-carbamates and other groups may be found in volume 3 of *The Peptides*, Gross, E. and Meinhofer, J. Academic Press, 1981 and *Protective Groups in Organic Synthesis*, Greene, T. W. John Wiley & Sons, New York, Chapter 7, 1981. The *N*-carbamate formation may be carried out in a solvent which does not adversely affect the reaction (e.g., acetone, dichloromethane, tetrahydrofuran, pyridine or *N,N*-dimethylformamide or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (cc), *N*-sulfenamides may be prepared from an amine and a sulfenyl halide (Davis, F. A.; Nadir, U. K. *Org. Prep. Proc. Int.* 1979, 11, 33; Kobayashi, T.; Iino, K.; Hiraoka, T. *J. Am. Chem. Soc.* 1977, 99, 5505; Zervas, L.; Borovas, D.; Gazis, E. *J. Am. Chem. Soc.* 1963, 85, 3660). Suitable reagents include, but are not limited to benzenesulfenyl halide, o-nitrobenzenesulfenyl halide, 2,4-dinitrosulfenyl halide, pentachlorobenzenesulfenyl halide, 2-nitro-4-methoxybenzenesulfenyl halide, triphenylmethylsulfenyl halide, and the like. Other groups may be found in volume 3 of *The Peptides*, Gross, E. and Meinhofer, J. Academic Press, 1981 and *Protective Groups in Organic Synthesis*, Greene, T. W. John Wiley & Sons, New York, Chapter 7, 1981. The *N*-sulfonylation may be carried out in a solvent which does not adversely affect the reaction (e.g., acetone, dichloromethane, tetrahydrofuran, pyridine or *N,N*-dimethylformamide or a mixture thereof). The reaction may be conducted above, at, or below ambient temperature.

In process (dd), -N=C=O may be prepared from an amine and oxalyl chloride, phosgene, diphosgene or triphosgene with or without the presence of a base (Weisenfeld, R.B., *J. Org. Chem.*, 51 (13): 2434-2436, 1986; Eckert, H., Forster, B., *Angew. Chemie*, IE, 26(9): 894-895, 1987; Arnold-Stanton, R., Lemal, D.J., *J. Org. Chem.*, 56(1), 146-151, 1991; Danda, H., Chino, K., Wake, S., *Chem. Exp.*, 6(4), 261-264, 1991). Suitable base for the reaction are triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine etc.

The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. ether, toluene, dichloromethane, chloroform,

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chlorobenzene etc.). The reaction may be conducted above, at, or below room temperature.

In process (ee), a -SePh group may be prepared by selective displacement of an -OS(O)₂F or -OS(O)₂CF₃ with benzeneselenol in the presence of a base.

5 Suitable bases for the reaction are triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine etc. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. ether, toluene, dichloromethane, chloroform, chlorobenzene etc.). The reaction may be conducted above, at, or below room temperature.

10 In process (ff), a -Se(O)Ph group may be prepared by selective oxidation of an -Se-Ph group with appropriate peroxides in the presence of a base.

Suitable peroxides are hydrogen peroxide, trifluoroperacetic acid, peracetic acid, or m-chloroperbenzoic acid, etc. Suitable base for the reaction are sodium bicarbonate, potassium bicarbonate, or cesium bicarbonate, etc. The 15 reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. ether, toluene, dichloromethane, chloroform, chlorobenzene etc.). The reaction may be conducted above, at, or below room temperature.

15 In process (gg), a compound of formulae IV, where one of R⁸ and R⁹ with one of R¹⁸ and R¹⁹ taken together form a bond, the others of R⁸, R⁹, R¹⁸ and R¹⁹ are hydrogen, by selective 1,2-elimination of an H-OSePh group in a corresponding compound containing an -Se(O)Ph group with or without the presence of base.

Suitable base for the reaction are sodium bicarbonate, potassium bicarbonate, or cesium bicarbonate, etc. The reaction may be carried out in a 25 solvent which does not adversely affect the reaction (e.g. ether, toluene, dichloromethane, chloroform, chlorobenzene etc.). The reaction may be conducted at or above room temperature.

20 In process (hh), selective oxidation of a double bond to form a 1,2-diol may be carried out using tertiary amine N-oxide-osmium tetroxide (VanRheenen, V., Kelly, R. C. and Cha, D. Y. *Tetrahedron Lett.*, 1976, 25, 1973-1976; Fraser-Reid, B., Molino, B. F., Magdzinski, L. and Mootoo, D. R. *J. Org. Chem.*, 1987, 52, 4505-4511); pyridine-osmium tetroxide (Cimino, G., Gavagnin, M., Sodano, G., Spinnella, A., Strazzullo, G., Schmitz, F. J. and Yalamanchili, G. *J. Org. Chem.*, 1987, 52, 2301-2303). chiral amine-osmium

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tetraoxide (Yamada, T. and Narasaka, K. *Chem. Lett.*, 1986, 131; Tokles, M. and Snyder, J. K. *Tetrahedron Lett.*, 1986, 27, 3957).

The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g., diethylether, dichloromethane, tetrahydrofuran, 5 acetonitrile, chloroform or *N,N*-dimethylformamide or a mixture thereof). The reaction may require cooling or heating, depending on the method chosen.

In process (ii), protection and derivatization for 1,2-diol may be carried out as cyclic acetals, cyclic ketals, cyclic ortho esters, cyclic boronates, cyclic carbonates, or as cyclic silyl derivatives. Suitable cyclic acetal and cyclic ketal formations may be carried out using a reaction of the diol and a carbonyl 10 compound in the presence of an acid catalyst (Fletcher, Jr. H. G *Methods Carbohydr. Chem.*, 1963, II, 307; Amarnath, V. and Broom, A. D. *Chem. Rev.*, 1977, 77, 183; Reese, C. B. *Tetrahedron*, 1978, 34, 3143 ; Clode, D. M. *Chem. Rev.* 1979, 79, 491 ; Hanessian, S., Chung, G. Y., Lavallee, P. and Pernet, A. G. 15 *J. Am. Chem. Soc.*, 1972, 94, 8929; Yuceer, L. *Carbohydr. Res.*, 1977, 56, 87.). Cyclic ortho ester formation, including cyclic orthoformates, may be carried out using a wide variety of reagents, but not limited to tetramethyl orthocarbonate-p-toluenesulfonic acid method (Niaz, G. R. and Reese, C. B. *J. Chem. Soc. Chem. Commun.*, 1969, 552), or acid catalyzed transketolization (Reese, C. B. 20 *Tetrahedron*, 1978, 34, 3143; Amarnath, V. and Broom, A. D. *Chem. Rev.*, 1977, 77, 183; Ahmad, M., Bergstrom, R. G., Cashen, M. J., Kresge, A. J., MacClelland, R. A. and Powell, M. F. *J. Am. Chem. Soc.*, 1977, 99, 4827). Cyclic carbonate may be prepared from 1,2-diol and phosgene or a chloroformate (Hough, L., Priddle, J. E. and Theobald, R. S. *Adv. Carbohydr. Chem.*, 1960, 15, 91-158 ; 25 Amarnath, V. and Broom, A. D. *Chem. Rev.*, 1977, 77, 183; Letsinger, R. L. and Ogilvie, K. K. *J. Org. Chem.*, 1967, 32, 296 ; Kutney, J. P. and Ratcliffe, A. H. *Synth. Commun.*, 1975, 5, 47.). Cyclic silyl derivatives of 1,2-diol may be prepared from the reaction using bis-(*tert*-butyl)dichlorosilane-triethylamine (*Tetrahedron Lett.*, 1981, 22, 4999), or diisopropylsilyl 30 bis(trifluoromethanesulfonate)-*tert*-amine (*Tetrahedron Lett.*, 1982, 23, 4871), and the like. Cyclic boronates formation may be carried out using following references (Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.*, 1978, 35, 31-80; Frechet, J. M. J., Nuyens, L. J. and Seymour, E. *J. Am. Chem. Soc.*, 1979, 101, 432).

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The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g., diethylether, dichloromethane, tetrahydrofuran, acetonitrile, chloroform or *N,N*-dimethylformamide or a mixture thereof). The reaction may require cooling or heating, depending on the method chosen.

5 In process (jj), suitable reducing agents are trialkylsilanes. Suitable acids are toluenesulfonic acid, trifluoroacetic acid, borotrifluoride etherate etc. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g., diethylether, dichloromethane, tetrahydrofuran, or chloroform or a mixture thereof). The reaction may be conducted at -50 to 0 °C.

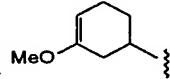
10 In process (kk), suitable alkylating agents are allyltrimethylsilane or alkyl alcohol. Suitable acids are toluenesulfonic acid, trifluoroacetic acid, borotrifluoride etherate etc. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g., diethylether, dichloromethane, tetrahydrofuran, or chloroform or a mixture thereof). The reaction may be 15 conducted at -50 to 0 °C.

In process (ll), a suitable reagent for activation of the alcohol of formula is fluorosulfonyl anhydride (prepared according to the procedure described by S. Kongpricha, W.G. Preusse and R. Schwarer, in Inorganic Synthesis, 1968, 11, p151-155) or trifluoromethanesulfonyl anhydride. The activation may be carried 20 out in a solvent which does not adversely affect the reaction (e.g. diethyl ether, dichloromethane, tetrahydrofuran, chloroform or *N*-methylpyrrolidone or a mixture thereof). The reaction may require cooling or heating, depending on the method used. Further, the reaction is preferably conducted in the presence of an organic or inorganic base such as cesium bicarbonate, pyridine, lutidine, 25 picoline, quinoline, diisopropylethylamine and the like. The reaction temperature is preferably from -100 to 30 °C, and more preferably from -78 to 0 °C. The reaction may require 20 minutes to 24 hours to complete, depending on the reagent chosen.

A suitable reagent for the dehydration of an activated alcohol is silica gel 30 or triethylamine. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. diethyl ether, dichloromethane, tetrahydrofuran, chloroform or toluene or a mixture thereof). The reaction may require cooling or heating, depending on the method used. The reaction temperature is preferably from -100 to 30 °C, and more preferably from -20 to 0

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°C. The reaction may require 20 minutes to 24 hours to complete, depending on

the conditions chosen. The hydrolysis of the dehydrated enol ether  may be carried out in dilute aqueous acid at room temperature.

In process (mm), a suitable acid for the rearrangement of the activated
 5 alcohol is silica gel. The reaction may be carried out in a solvent which does not
 adversely affect the reaction (e.g. diethyl ether, dichloromethane,
 tetrahydrofuran, chloroform or toluene or a mixture thereof). The reaction may
 require cooling or heating, depending on the method used. The reaction
 temperature is preferably from -100 to 30 °C, and more preferably from -20 to 0
 10 °C. The reaction may require 20 minutes to 24 hours to complete, depending on
 the conditions

It should be noted that numerous asymmetric centers may exist in the
 compounds of the present invention. Except where otherwise specified, the
 present invention contemplates the various stereoisomers and mixtures thereof.
 15 It should also be noted that certain variable elements of the structural formulae
 herein, such as the radicals R¹¹, R²⁰, R²⁴, R²⁵, R²⁶ and R²⁷ or the subscript
 integers m and s, may appear more than once in a particular formula. In such
 instances, it is intended that, within a single formula, the values of these
 variables may be the same or different at each occurrence.

20

The present invention can be illustrated by the following non-limiting,
 representative examples. In the following examples, unless states otherwise,
 R^{10a} = -OCH₃ and R^{10b} = H.

The following abbreviations are used: DDQ for 2,3-dichloro-5,6-dicyano-
 25 1,4-benzoquinone, EDAC for 1-ethyl-3-(3'-dimethylamino)-propylcarbodiimide,
 EtOAc for ethyl acetate, EtOH for ethanol, HOBt for 1-hydroxybenzotriazole,
 and MeOH for methanol.

Example 1

30 Formula VI: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R = F; R⁹ = H

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Fluorosulfonyl anhydride (0.17 g, in 1 mL of dry CH₂Cl₂) was added into a stirred solution of rapamycin (0.457 g) and 2,6-lutidine (0.22 g) in dry dichloromethane (5 mL) at -70 °C. After being stirred at -70 °C for 1 hour, the reaction mixture was partitioned between ether and ice-cold 0.1 N hydrochloric acid. The organic phase was washed once with saturated brine, dried over magnesium sulfate and filtered through silica gel (2 g) eluting with ether. The solvent was removed *in vacuo*, and the product was stored in the freezer.

Example 2

10 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O;
 R⁸ = -OC(=O)-O(p-Nitro-phenyl); R⁹ = -H

15 4-Nitrophenyl chloroformate (0.5 g) was added into a stirred solution of rapamycin (0.9 g) in dry pyridine (2 mL) at room temperature. After being stirred at 40-50 °C for 0.5 hour, the reaction was cooled to 0 °C and partitioned between ether and ice-cold 0.4 N hydrochloric acid. The organic phase was washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The product was purified by silica gel chromatography (20 g) eluting with 20% acetone/hexanes to afford 0.72 g of the title compound. MS (FAB)
20 *m/z: M+K= 1117.*

Example 3

25 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
 R⁶ and R⁷ taken together = O; X and Y taken together = O;
 R⁸ = -OC(=O)-morpholine; R⁹ = -H

To the compound resulting from Example 2 (514.5 mg) dissolved in 3.5 mL of anhydrous dichloromethane at 0 °C was added morpholine (250 µL). The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was purified by silica gel chromatography (70 g) eluting with 25% acetone/hexanes to give 343.2 mg of the title compound. m.p. 115-199 °C. MS (FAB) *m/z: M+K= 1065.*

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Example 4

5 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O; R⁶
and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-O(N-succinimidyl); R⁹ = -H

The title compound is prepared from rapamycin and di-(N-succinimidyl)-carbonate in pyridine according to the procedure described in Example 2.

10

Example 5

Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-(N-triazole); R⁹ = -H

15 The title compound is prepared from rapamycin and 1,1'-carbonyldi(1,2,4-triazole) in pyridine according to the procedure described in Example 2.

Example 6

20 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-(N-imidazole); R⁹ = -H

25 The title compound is prepared from rapamycin and 1,1'-carbonyldiimidazole in pyridine according to the procedure described in Example 2.

25

Example 7

30 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O; R⁶
and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-O(hydroxy-benzotriazole); R⁹ = -H

30 The title compound is prepared from rapamycin and 1,1'-carbonyldi(hydroxybenzotriazole) in pyridine according to the procedure described in Example 2.

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Example 8

5 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-piperidine; R⁹ = -H

The title compound is prepared from the compound resulting from Example 2 and piperidine according to the procedure described in Example 3.

10

Example 9

Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -H;
R⁹ = -O-formyl

15 The title compound of Example 1 is dissolved in N,N-dimethylformamide and stirred at room temperature overnight. The reaction mixture is partitioned between ether and water. The organic phase is washed once with brine, dried over magnesium sulfate, and solvent removed *in vacuo*. The product is purified by silica gel chromatography eluting with 30% acetone/hexanes.

20

Example 10

Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -H; R⁹ = -OH

25 To a solution of rapamycin (505.4 mg) in 4 mL of methylene chloride cooled to -78 °C was added 140 µL of 2,6-lutidine followed by 100 µL of (FSO₂)₂O in 1 mL of methylene chloride. The reaction mixture was stirred at -78 °C for 15 minutes after the addition was complete. The reaction mixture was partitioned between ether and 0.1 N HCl. The organic layer was washed with 20 mL of water and 20 mL of saturated NaCl solution, dried over magnesium sulfate and passed through a silica gel plug eluting with cold ether. The solvent was removed *in vacuo*, and the residue was dissolved in 10 mL of a 1:1 mixture of THF and DMSO. After stirring at room temperature for 10 minutes, the reaction mixture was stored in the refrigerator for 2 days. Water (2 mL) was added, and the reaction mixture was stirred at room temperature for 1 hour. A

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solution was 500 mg of NaHCO₃ in water (50 mL) was added, and the mixture was extracted with Et₂O (3 x 70 mL). The combined organic extracts were washed with 50 mL of dilute NaHCO₃ solution, 50 mL of water, and 50 mL of saturated NaCl solution, dried over MgSO₄ and concentrated *in vacuo*. The residue obtained was chromatographed on a silica gel (15 g) column eluting with 4% isopropanol in dichloromethane to give 271 mg of the title compound. m.p. 90-93 °C. MS (FAB) *m/z*: M+K= 952. Selected CMR (CDCl₃): 215.2, 208.1, 192.8, 169.7, 169.3, 166.7, 140.5, 140.1, 136.0, 135.7, 133.6, 133.3, 130.2, 129.5, 129.0, 126.7, 126.4, 98.7, 98.5, 86.4, 84.9, 84.3, 80.6, 77.2, 75.6, 67.8, 67.2, 65.5, 59.3, 59.0, 56.4, 55.9, 51.3, 46.5, 46.0, 44.2, 41.4, 40.7, 40.2, 39.0, 38.7, 35.6, 35.2, 34.4, 33.8, 33.1, 32.9, 32.4, 31.4, 30.9, 29.6, 27.2, 27.1, 25.3, 24.4, 21.5, 20.7, 16.3, 16.2, 16.0, 15.9, 13.7, 13.2 and 10.2.

Example 11

15 Formula I: R¹= methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -H;
R⁹ = -OC(=O)-O(p-Nitro-phenyl)

The title compound is prepared from the compound resulting from Example 10 and 4-nitophenyl chloroformate according to the procedure described in Example 2.

Example 12

25 Formula I: R¹= methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -H;
R⁹ = -OC(=O)-morpholine

The title compound is prepared from the compound resulting from Example 11 and morpholine according to the procedure described in Example 3.

Example 13

30 Formula VI: R¹= methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁹=H; R = -CF₃

Trifluoromethanesulfonyl anhydride (0.2 g) in 1 mL of dry CH₂Cl₂ was added into a stirred solution of rapamycin (0.457 g) and 2,6-lutidine (0.22 g) in dry dichloromethane (5 mL) at -70 °C. After being stirred at that temperature for

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1 hour, the reaction mixture was partitioned between ether and ice-cold 0.1 N hydrochloric acid. The organic phase was washed once with saturated brine, dried over magnesium sulfate and filtered through silica gel (2 g) eluting with ether. The solvent was removed *in vacuo*, and the product was stored in the
5 freezer.

Example 14

Formula I: R^1 = methyl; R^2 = -H; R^3 = -OH; R^4 and R^5 taken together = O;
10 R^6 and R^7 taken together = O; X and Y taken together = O; R^8 = -H;
 R^9 = $-\text{OS}(\text{O})_2\text{F}$

The title compound is prepared from the compound resulting from Example 10 and fluorosulfonyl anhydride according to the procedure described in Example 1.

15 Example 15

Formula I: R^1 = methyl; R^2 = -H; R^3 = -OH; R^4 and R^5 taken together = O;
20 R^6 and R^7 taken together = O; X and Y taken together = O; R^8 = -H;
 R^9 = $-\text{OS}(\text{O})_2\text{CF}_3$

The title compound is prepared from the compound resulting from Example 10 and trifluoromethanesulfonyl anhydride according to the procedure described in Example 1.

Example 16

25 Formula V: R^1 = methyl; R^2 = -H; R^3 = -OH; R^4 and R^5 taken together = O;
 R^6 and R^7 taken together = O; X and Y taken together = O;
 R^8 = $-\text{OC}(=\text{O})-\text{NMe(OH)}$; R^9 = -H

The title compound was prepared from the compound resulting from Example 2 and N-methyl hydroxylamine according to the procedure described in Example 3.

30

Example 17

Formula V: R^1 = methyl; R^2 = -H; R^3 = -OH; R^4 and R^5 taken together = O;
35 R^6 and R^7 taken together = O; X and Y taken together = O;
 R^8 = $-\text{OC}(=\text{O})-\text{NMe(OMe)}$; R^9 = -H

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To N,O-dimethylhydroxylamine hydrochloride 449.8 mg, 4.6 mmol) was added pyridine (5 mL), and the mixture was stirred at room temperature for 1 hour. To this solution was added the compound resulting from Example 2 (826.2 mg, 0.701 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 5 room temperature overnight. The reaction mixture was partitioned between 0.5 N HCl and Et₂O. The organic phase was washed with saturated NaCl solution, dried over MgSO₄ and passed through a short column of silica gel (10 g). The partially purified compound was further purified by HPLC (Rainin Microsorb silica gel) eluting with 75% acetone in hexane to afford the title compound. m.p. 10 105-109 °C. MS (FAB) *m/z*: M+K= 1039. Selected CMR (CDCl₃): 215.5, 208.1, 207.6, 192.5, 169.8, 169.2, 166.8, 156.9, 140.8, 140.2, 136.1, 135.5, 133.7, 133.4, 130.1, 130.0, 129.6, 129.3, 126.7, 126.4, 98.5, 86.5, 84.9, 84.4, 81.1, 78.1, 77.2, 75.5, 67.8, 67.2, 61.5, 59.3, 57.6, 56.2, 55.9, 51.3, 46.6, 46.1, 44.2, 41.4, 40.7, 40.2, 38.9, 38.3, 36.1, 35.6, 35.1, 34.6, 33.8, 33.3, 33.0, 32.9, 15 31.6, 31.3, 30.1, 27.9, 27.3, 27.0, 25.3, 24.3, 22.6, 21.7, 21.5, 20.7, 16.2, 16.1, 15.9, 15.0, 14.1, 13.8, 13.1 and 10.2.

Example 18

20 Formula V: R¹= methyl; R²= -H; R³= -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸= -OC(=O)-NH(OBn); R⁹= -H

The title compound is prepared from the compound resulting from Example 2 and
O-benzylhydroxylamine according to the procedure described in Example 3.
25

Example 19

30 Formula VII: R¹= methyl; R²= -H; R³= -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸= -OC(=O)-(N-methylpiperazine); R⁹= -H

The title compound is prepared from the compound resulting from Example 2 and
N-methyl piperazine according to the procedure described in Example 3.

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Example 20

5 Formula I: R¹ = methyl; R² = -H; R³ = -OAc; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -OH; R⁹ = -H

The title compound is prepared according to EP 0507556 (Example 4).

Example 21

10 Formula I: R¹ = methyl; R² = -H; R³ = -O-(tert-butyldimethylsilyl);
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -O-(tert-butyldimethylsilyl); R⁹ = -H

The title compound is prepared from rapamycin according to EP 0507556
(Example 4).

15 Example 22

Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = NNMe₂; X and Y taken together = O; R⁸ = -OH;
R⁹ = -H.

20 The title compound is prepared from rapamycin according to EP 0507556
(Example 1).

Example 23

25 Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = NNMe₂; X and Y taken together = O; R⁸ = -H;
R⁹ = -OH

30 The title compound is prepared from the compound resulting from
Example 10 (42-epi-rapamycin) and N,N-dimethylhydrazine according to the
procedure described in Example 5 of U.S. patent No. 5,120,726, which is
incorporated herein by reference.

Example 24

Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = N-OMe; X and Y taken together = O; R⁸ = -H;
R⁹ = -OH

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The title compound is prepared from rapamycin and O-methylhydroxylamine according to the procedure described in Example 5 of U.S. patent 5,120,726 and UK Patent GB 2,247,017A which are incorporated herein by reference.

5

Example 25

Formula I: R¹ = methyl; R² = -H; R³ = -O-(tert-butyldimethylsilyl);
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OH; R⁹ = -H.

10 Two equivalents of 48% aqueous HF in acetonitrile is added dropwise into a stirred solution of the compound resulting from Example 21 in acetonitrile at 0 °C. After being stirred at that temperature for 1 hour, powdered sodium bicarbonate is added and stirred for another 0.5 hour. The solids are filtered off and the product is purified by silica gel chromatography.

15

Example 26:

Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = N-OMe; X and Y taken together = O; R⁸ = -H;
R⁹ = -OS(O)₂F

20 The title compound is prepared from the compound resulting from Example 24 and fluorosulfonyl anhydride according to the procedure described in Example 1.

Example 27

25 Formula VI: R¹ = methyl; R² = -H; R³ = tert-butyldimethylsiloxy;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R = F; R⁹ = H

30 The title compound is prepared from the compound resulting from Example 25 and fluorosulfonyl anhydride according to the procedure described in Example 1.

Example 28

5 Formula VI: R¹ = methyl; R² = -H; R³ = -OAc; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R = F; R⁹ = H

The title compound is prepared from the compound resulting from Example 20 and fluorosulfonyl anhydride according to the procedure described in Example 1.

10

Example 29:

Formula I: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = N-OMe; X and Y taken together = O; R⁸ = -H;
R⁹ = -OC(=O)-O(p-Nitro-phenyl).

15 The title compound is prepared from the compound resulting from Example 24 and
4-nitrophenyl chloroformate according to the procedure described in Example 2.

Example 30

20 Formula VII: R¹ = methyl; R² = -H; R³ = -O-(tert-butyldimethylsilyl);
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OC(=O)-O-(p-Nitro-phenyl); R⁹ = -H

The title compound is prepared from the compound resulting from Example 25 and
4-nitrophenyl chloroformate according to the procedure described in Example 2.

25

Example 31

Formula VII: R¹ = methyl; R² = -H; R³ = -OAc; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-O-(p-Nitro-phenyl); R⁹ = -H

30 The title compound is prepared from the compound resulting from Example 20 and
4-nitrophenyl chloroformate according to the procedure described in Example 2.

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Example 32

5 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = N-OMe; X and Y taken together = O;
R⁸ = -OC(=O)-morpholine; R⁹ = -H

The title compound is prepared from the compound resulting from Example 29 and morpholine according to the procedure described in Example 3.

10

Example 33

Formula VII: R¹ = methyl; R² = -H; R³ = -O-(tert-butyldimethylsilyl); R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-morpholine; R⁹ = -H

15

The title compound is prepared from the compound resulting from

Example 30 and morpholine according to the procedure described in Example 3.

Example 34

20

Formula VII: R¹ = methyl; R² = -H; R³ = -OAc; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-morpholine; R⁹ = -H

The title compound is prepared from the compound resulting from

Example 31 and morpholine according to the procedure described in Example 3.

Example 35

25

Formula IVc: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ and R⁹ taken together = O

30

Silica gel (25 g) was added to a solution of the compound resulting from Example 13 (prepared from 0.53 g of rapamycin) in ether at 0 °C. The solvent was then removed *in vacuo*, and the resulting powder was refrigerated for 8 days at 8 °C. The product on silica gel was eluted with acetone and the solvent removed *in vacuo*. The crude product was purified by HPLC (Rainin Microsorb silica gel) eluting with 30% acetone/ hexanes. MS (FAB) *m/z*: M+K= 920.

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Example 36

5 Formula IVa: R¹= methyl; R²= -H; R³= -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O

Silica gel (25 g) was added to a solution of the compound resulting from Example 13 (prepared from 0.53 g of rapamycin) in ether at 0 °C. The solvent was then removed *in vacuo*, and the resulting powder was refrigerated for 8 days at 8 °C. The product on silica gel was eluted with acetone and solvent removed
10 *in vacuo*. The crude product was purified by HPLC (Rainin Microsorb silica gel) eluting with 30% acetone/ hexanes. MS (FAB) *m/z*: M+K= 934.

Example 37

15 Formula IVb: R¹= methyl; R²= -H; R³= -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = R¹⁸ = -H;
R⁹ and R¹⁹ taken together form a bond

The title compound was isolated from the reaction mixture on silica gel of Example 36. MS (FAB) *m/z*: M+K= 934.

20

Example 38

Formula II: R¹= methyl; R²= -H; R³= -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -H;
R⁹ = -S-(2'-imidazole)

To a solution of rapamycin (838 mg, 0.917 mmol) in 5 mL of methylene chloride was added 450 µL of 2,6-lutididine at -78 °C followed by (FSO₂)₂O (200 µL). The reaction mixture was stirred for 20 minutes under a nitrogen atmosphere and then 204 mg of 2-mercaptoimidazole in 5 mL of THF was added. The reaction mixture was allowed to warm to room temperature and stirred overnight under nitrogen. The reaction mixture was partitioned between
25 150 mL of water and a mixture of 21:1 EtOAc and Et₂O. The aqueous phase was extracted with two 100 mL portions of the organic solvent mixture. The combined organic extracts were washed twice with water and once with saturated sodium chloride solution, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified on a silica gel column eluting with 1:1 acetone-hexane to
30

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give 380 mg of partially purified material which was further purified by HPLC eluting with 5% isopropanol in methylene chloride. m.p. 122-126 °C. MS (FAB) m/z : M+K= 1034.

5

Example 39

Formula II: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = -H;
R⁹ = -S-(2'-N-methyl-imidazole)

To a solution of rapamycin (639 mg, 0.699 mmol) in 10 mL of methylene chloride was added 250 μ L of 2,6-lutididine at -78 °C followed by (FSO₂)₂O (160 μ L). The reaction mixture was stirred for 20 minutes under a nitrogen atmosphere and then partitioned between ether and 0.1 N HCl. The organic phase was passed through a silica gel plug eluting with Et₂O. This activated intermediate was dissolved in methylene chloride (8 mL), cooled to -78 °C, and treated with 2,6-lutidine (250 μ L) followed by 1-methyl-2-mercaptoimidazole (171.4 mg). The reaction mixture was stirred under a nitrogen overnight and then partitioned between Et₂O and 0.1 N HCl. The organic phase was concentrated *in vacuo*, and the residue obtained purified on a silica gel column eluting with 4% isopropanol in methylene chloride to give 159 mg of the title compound. m.p. 111-116 °C. MS (FAB) *m/z*: M+K= 1048.

Example 40

Formula VII: R¹ = methyl; R² = R⁹ = H, R³ = OH, R⁴ and R⁵ taken together are oxo; R⁶ and R⁷ taken together are oxo; X and Y taken together are oxo;
R⁸ = OCH₂C(O)NHPH

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Example 41

Formula VII: R¹=methyl; R²=R⁹=H, R³=OH, R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are oxo; X and Y taken together are oxo;
R⁸=OCH₂C(O)N(CH₂CH₂)₂O

5 A solution of rapamycin (0.58 g, 0.63 mmol) in dichloromethane (10 mL) containing rhodium(II)acetate dimer (3 mg) is refluxed while morpholino-diazoacetate (98 mg, 0.63 mmol) in dichloromethane (1 mL) is added dropwise. After complete addition the reaction is refluxed for 30 minutes and additional
10 morpholino-diazoacetate (196 mg, 1.26 mmol) in dichloromethane (1.5 mL) is added dropwise with reflux continuing 30 minutes after complete addition. The solvent is removed *in vacuo* and the residue purified by HPLC on silica gel. Fractions containing desired product are pooled, and concentrated, to constant weight under high vacuum to give the desired product .

15

Example 42

Formula VII: R¹= methyl; R²=R⁹= -H; R³ = -OH;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OCH₂C(O)NH(4-Cl-Ph)

20 A solution of rapamycin (0.58 g, 0.63 mmol) in dichloromethane (10 mL) containing rhodium(II)acetate dimer (3 mg) is stirred at 0 °C while N-p-Cl-phenyl diazoacetamide (101 mg, 0.63 mmol) in dichloromethane (1 mL) is added dropwise (24 hours). After complete addition the reaction is maintained at 0 °C for an additional 24 hours. The solvent is removed *in vacuo* and the residue
25 purified by chromatography on silica gel to provide the title compound.

Example 43

Formula VII: R¹= methyl; R²=R⁹= -H; R³ = -OH;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OCH₂C(O)NR²⁴R²⁵,
where R²⁴R²⁵ taken together is (CH₂CH₂)₂O.

30

The title compound is prepared using the procedure described in Example 42 and substituting 4-(2-diazo-1-oxo-ethyl)-morpholine for N-phenyl diazoacetamide.

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Example 44

5 Formula VII: R¹ = methyl; R² = R⁹ = -H; R³ = -OH;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken
together = O; R⁸ = -OCH₂C(O)NHCH₂CH₂CH₂OC(O)CH₃.

The title compound is prepared using the procedure described in Example 42 and substituting N-(3-acetyloxypropyl)-diazoacetamide for N-phenyl diazoacetamide.

10

Example 45

Formula VII: R¹ = methyl; R² = R⁹ = -H; R³ = -OH;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OCH₂C(O)NH(4-pyridyl).

15 The title compound is prepared using the procedure described in Example 42 and substituting N-(4-pyridyl)-diazoacetamide for N-phenyl diazoacetamide.

Example 46

20 Formula VII: R¹ = methyl; R² = R⁹ = -H; R³ = -OH;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OCH₂C(O)NHCH₂C(O)O(fluorenylmethyl).

The title compound is prepared using the procedure described in Example 42 and substituting N-(2-(fluorenylmethoxy)-2-oxo-ethyl)-diazoacetamide for N-phenyl diazoacetamide.

25

Example 47

Formula VII: R¹ = methyl; R² = R⁹ = -H; R³ = -OH;
R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O;
X and Y taken together = O; R⁸ = -OCH₂C(O)NHCH₂C(O)OH

30 The compound resulting from Example 46 is dissolved in dichloromethane and treated with 1 equivalent of piperidine. After complete consumption of starting material, as evidenced by TLC, the material is purified by chromatography on silica gel to provide the title compound.

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Example 48

5 Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-N(2'-pyridylmethyl)(N,N-dimethylaminopropyl); R⁹ = -H

The title compound is prepared from the compound resulting from Example 2 and N-(2'-pyridylmethyl),N-(N,N-dimethylaminopropyl)amine according to the procedure described in Example 3.

10

Example 49

Formula VII: R¹ = methyl; R² = -H; R³ = -OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O;
R⁸ = -OC(=O)-N(phenyl)-(N,N-dimethylaminopropyl); R⁹ = -H

15 The title compound is prepared from the compound resulting from Example 2 and N-(phenyl)-N-(N,N-dimethylaminopropyl)amine according to the procedure described in Example 3.

Example 50

20 Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = N₃;
R^{10a} = OCH₃; R^{10b} = H

25 To a solution of the compound resulting from Example 13 (937.2 mg, 1.02 mmol) in 5 mL of acetone was added sodium azide (355.6 mg, 5.47 mmol) in 0.5 mL of water. The reaction mixture was stirred overnight at room temperature. Additional water (1 mL) was added, and the reaction mixture was stirred at room temperature for an additional 1 day. Anhydrous sodium sulfate (2 g) was added and stirring was continued for 30 minutes. The crude mixture was then passed through a silica gel column. This partially purified material was rechromatographed on silica gel eluting with 35% acetone in hexane to obtain 30 the title compound (380 mg, 40%) which was recrystallized from ether. m.p. 141-146 °C (dec). MS (FAB) *m/z*: M + K = 977.

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Example 51

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = NH₂;
R^{10a} = OCH₃; R^{10b} = H

To a solution of the compound resulting from Example 50 (100 mg, 0.107 mmol) in 1 mL of THF containing 0.2 mL of water was added triphenylphosphine (0.25 g, 0.954 mmol). The reaction mixture was stirred at room temperature for 3 days and then concentrated *in vacuo*. The residue was partitioned between Et₂O and water. The organic phase was dried over magnesium sulfate, concentrated *in vacuo* and purified by silica gel chromatography to afford the title compound. MS (FAB) *m/z*: M+K= 951.

Example 52

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = NHAc;
R^{10a} = OCH₃; R^{10b} = H

Acetic anhydride (0.15 mL) is added into a solution of the compound resulting from Example 51 (1 g) in dichloromethane (5 mL) followed by N-methylmorpholine (0.5 mL) at 0 °C. After stirring at that temperature for 30 minutes, the reaction mixture is partitioned between ether and 0.1 N hydrochloric acid. The organic phase is washed once with brine, dried over magnesium sulfate and the solvent removed *in vacuo*. The crude product is purified by silica gel chromatography eluting with 50% acetone in hexanes.

25

Example 53

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = NCO;
R^{10a} = OCH₃; R^{10b} = H

30 A solution of triphosgene (0.15 g) in 2 mL dry dichloromethane is added into a stirred solution of the compound resulting from Example 51 (1 g) in pyridine (10 mL) at 0 °C. After being stirred at that temperature for 3 hours, the reaction is partitioned between ether and 0.1 N hydrochloric acid. The organic phase is washed once with brine, dried over magnesium sulfate and solvent

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removed *in vacuo*. The product is purified by silica gel chromatography eluting with 50% acetone in hexanes.

Example 54

5 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = NHSO₂Ph; R^{10a} = OCH₃; R^{10b} = H

10 The title compound is prepared from the compound resulting from Example 52, benzenesulfonyl chloride and N-methylmorpholine in dichloromethane according to the procedure described in Example 52.

Example 55

15 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = NHC(O)NHPH; R^{10a} = OCH₃; R^{10b} = H

20 Phenyl isocyanate (0.15 mL) is added into a solution of the compound resulting from Example 51 (1 g) in tetrahydrofuran (5 mL) followed by N-methylmorpholine (0.3 mL) at 50 °C. After being stirred at that temperature for 30 minutes, the reaction mixture is partitioned between ether and 0.1 N hydrochloric acid. The organic phase is washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The crude product is purified by silica gel chromatography eluting with 50% acetone in hexanes.

Example 56

25 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = NHC(=O)NH-NMe₂; R^{10a} = OCH₃; R^{10b} = H

30 1,1-Dimethylhydrazine (0.07 g) is added into a solution of the compound resulting from Example 54 (1 g) in pyridine (5 mL) at 0 °C and refrigerated overnight. Pyridine is removed *in vacuo*, and the crude mixture is purified by silica gel chromatography eluting with 65% acetone in hexanes.

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Example 57

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = Se-Ph;
R^{10a} = OCH₃; R^{10b} = H

5 Benzeneselenol (0.2 mL) is added into a stirred solution of the title compound of Example 1 (1 g) and diisopropylethylamine (0.2 mL) in dry tetrahydrofuran (5 mL) at 0 °C. After being stirred at that temperature for 2 hours, the reaction mixture is partitioned between ether and 0.1 N hydrochloric acid. The organic phase is washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The product is purified by silica gel chromatography eluting with 40% acetone in hexanes.

10

Example 58

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = Se(O)-Ph;
R^{10a} = OCH₃; R^{10b} = H

15 3-Chloroperoxybenzoic acid (50-60%, 0.5 g) is added into a stirred suspension of the compound resulting from Example 56 (1 g) and powdered cesium carbonate (1 g) in dichloromethane (10 mL) at 0 °C. After being stirred at that temperature for 1 hour, the reaction mixture is partitioned between ethyl acetate and 0.1 N sodium bicarbonate. The organic phase is washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The product is purified by silica gel chromatography eluting with 50% acetone in hexanes.

20

25 Example 59

Formula IVb: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R^{10a} = OCH₃;
R^{10b} = H; R⁸ = R¹⁸ = OH, R⁹ = R¹⁹ = H

30 N-Methylmorpholine N-oxide (0.26 g) is added into a stirred mixture of the compound resulting from Example 37 (0.9 g) and osmium tetroxide (0.03 mL, 4% solution in water) in tetrahydrofuran (20 mL) at room temperature for 7 days. The reaction mixture is partitioned between ether and 1 N sodium hydrogen sulfite. The organic phase is washed once with brine, dried over

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magnesium sulfate and the solvent removed *in vacuo*. The product is purified by silica gel chromatography eluting with 50% acetone in hexanes.

Example 60

5 Formula IVb: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R^{10a} = OCH₃;
R^{10b} = H; R⁸ = R¹⁸ = H; R⁹ and R¹⁹ taken together form a cyclic carbonate

A solution of triphosgene (0.15 g) in 2 mL dry dichloromethane is added into a stirred solution of the compound resulting from Example 58 (1 g) in
10 pyridine (10 mL) at 0 °C. After stirring at that temperature for 3 hours, the reaction is partitioned between ether and 0.1 N hydrochloric acid. The organic phase is washed once with brine, dried over magnesium sulfate and the solvent removed *in vacuo*. The product is purified by silica gel chromatography eluting with 50% acetone in hexanes.

15

Example 61

Formula IVb: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶
and R⁷ taken together = O; X and Y taken together = O; R^{10a} = OCH₃; R^{10b} =
H; R⁸ = R¹⁸ = H;
20 R⁹ and R¹⁹ taken together form a cyclic sulfate

The title compound is prepared from the compound resulting from Example 58 and sulfonyl chloride in pyridine according to the procedure described in Example 59.

25

Example 62

Formula IVb: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R^{10a} = OCH₃;
R^{10b} = H; R⁸ = R¹⁸ = H; R⁹ and R¹⁹ taken together form a cyclic sulfite

30 The title compound is prepared from the compound resulting from Example 58 and thionyl chloride in pyridine according to the procedure described in Example 59.

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Example 63

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = -SC(=NH)NH₂; R^{10a} = OCH₃; R^{10b} = H.

5 Powdered thiourea (0.106 g) was added into a stirred solution of the compound resulting from Example 13 (0.94 g) and 2,6-lutidine (0.3 mL) at -78 °C and allowed to warm up to room temperature. After stirring at room temperature for 16 hours, the solvent was removed *in vacuo*, and the product was used in next step without further purification.

10

Example 64

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = SH; R^{10a} = OCH₃; R^{10b} = H

15 The compound resulting from Example 63 was added 85 μL (1 equivalent) of morpholine at room temperature. After stirring for two hours, an additional 20 μL of morpholine was added and stirring was continued for an additional hour. An additional aliquot of morpholine (60 μL) was added and stirring was continued for an additional 30 minutes. The reaction mixture was
20 partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the title compound (189 mg). m.p. 105-111 °C. MS (FAB) *m/z*: M + K = 968.

25

Example 65

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = -SC(=NNH₂)NH₂; R^{10a} = OCH₃; R^{10b} = H

30 Powdered thiosemicarbazide (0.106 g) is added into a stirred solution of the compound resulting from Example 13 (0.94 g) and 2,6-lutidine (0.3 mL) at -78 °C and allowed to warm to room temperature. After stirring at room temperature for 16 hours, the solvent is removed *in vacuo*, and the product is purified by silica gel chromatography eluting with 5 % isopropanol in dichloromethane.

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Example 66

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = -SCH₂CO₂Et; R^{10a} = OCH₃; R^{10b} = H

5

Ethyl bromoacetate (0.2 mL) is added into a stirred solution of the compound resulting from Example 64 (1 g) and 2,6-lutidine (0.2 g) in acetonitrile under nitrogen at room temperature. After stirring at room temperature for 5 hours, the solvent is removed *in vacuo*, and the product is purified by silica gel chromatography eluting with 40% acetone in hexanes.

10

Example 67

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = 4'-PyridylCH₂S-; R^{10a} = OCH₃; R^{10b} = H

15

The title compound is prepared from the compound resulting from Example 64, 4-picoly l chloride hydrochloride and 2,6-lutidine in acetonitrile at 60 °C according to the procedure described in Example 66.

20

Example 68

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = 3'-PyridylCH₂S-; R^{10a} = OCH₃; R^{10b} = H

25

The title compound is prepared from the compound resulting from Example 64, 3-picoly l chloride hydrochloride and 2,6-lutidine in acetonitrile at 60 °C according to the procedure described in Example 66.

Example 69

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = 2'-PyridylCH₂S-; R^{10a} = OCH₃; R^{10b} = H

30

The title compound is prepared from the compound resulting from Example 64, 2-picoly l chloride hydrochloride and 2,6-lutidine in acetonitrile at 60 °C according to the procedure described in Example 66.

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Example 70

Formula II: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
5 R⁹ = -SCH₂COCO₂Et; R^{10a} = OCH₃; R^{10b} = H

The title compound is prepared from the compound resulting from Example 64, ethyl bromopyruvate and 2,6-lutidine in acetonitrile at 60 °C according to the procedure described in Example 66.

10

Example 71

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -(pyridin-4-on-1-yl); R^{10a} = OCH₃; R^{10b} = H

To a solution of the compound resulting from Example 13 (1.01 mmol) 15 and 2,6-lutidine (0.2 mL) in methylene chloride (2 mL) was added 4-hydroxypyridine (0.5132 g) in 2 mL of THF containing 0.5 mL of methanol. The reaction mixture was stirred at room temperature for 36 hours and then chromatographed on silica gel eluting with 50% acetone in hexanes to afford 0.277 g of the title compound. m.p. 126-131 °C. MS (FAB) m/z: M + K = 1029.

20

Example 72

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O; R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -(pyridin-2-on-1-yl); R^{10a} = OCH₃; R^{10b} = H

25 To a solution of the compound resulting from Example 13 (924 mg, 0.88 mmol) in 5 mL of THF was added 0.25 mL of 2,6-lutidine followed by 511.2 g of 2-hydroxypyridine (0.5112 g) in dichloromethane-tetrahydrofuran (1:1, 4 mL). The reaction mixture was stirred at room temperature overnight and then chromatographed on silica gel eluting with 50% acetone in hexanes to afford 30 0.45 g of the title compound. m.p. 101-106 °C. MS (FAB) m/z: M + K = 1029.

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Example 73:

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;

R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;

R⁹ = the ethylene ketal of pyridin-4-on-1yl; R^{10a} = OCH₃; R^{10b} = H

5 A suspension of 4-(hydroxethoxy)pyridine (0.51 g) in 1:1 dichloromethane-tetrahydrofuran (4 mL) is added into a stirred solution of the compound resulting from Example 13 (0.95 g) and 2,6-lutidine (0.2 mL) in dry tetrahydrofuran at room temperature. After stirring at room temperature for 36 hours, the reaction mixture is chromatographed on silica gel eluting with 50%
10 acetone in hexanes to afford the title compound.

Example 74

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;

R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = OCH₃;

15 R^{10a} = OCH₃; R^{10b} = H
To a solution of the compound resulting from Example 13 (1.21 g, 1.11 mmol) in 5 mL of THF was added 0.25 mL of 2,6-lutidine followed by 0.87 g (6.26 mmol) of 4-(2-hydroxyethyl)pyridine and 0.5 mL of methanol. The reaction mixture was stirred at room temperature under nitrogen overnight and then poured onto a silica gel column and eluted with 35% acetone in hexanes to give partially purified material. This material was rechromatographed on silica gel eluting with 25% acetone in hexanes to afford 462 mg. This material was rechromatographed on silica gel eluting with 1:1 ethyl acetate-hexane to afford 108 mg of pure title compound. m.p. 102-106 °C. MS (FAB) *m/z*: M + K = 966.
20
25

Example 75

Formula VII: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;

R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = OCH₂SCH₃;

R⁹ = H; R^{10a} = OCH₃; R^{10b} = H

30 To a solution of rapamycin (1.0349 g) in DMSO (3 mL) was added acetic anhydride (3 mL) and 0.5 mL methylene chloride. The reaction mixture was stirred one day at room temperature and then partitioned between ether and water. The organic phase was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting

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with 25% acetone in hexanes to afford partially purified compound which was rechromatographed on silica gel eluting with 2% isopropanol in methylene chloride to give pure title compound (270.7 mg). m.p. 94-98 °C. MS (FAB) *m/z*: M + K = 1012.

5

Example 76

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = OCH₂SCH₃; R^{10a} = OCH₃; R^{10b} = -H

10 The compound resulting from Example 1 (1 g) is dissolved in anhydrous dimethyl sulfoxide (1.5 mL), and the mixture is stirred at room temperature for 14 hours. The reaction mixture is partitioned between ether and water. The organic phase is washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The product is purified by silica gel chromatography
15 eluting with 40% acetone in hexanes.

Example 77

Formula VII: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = OH; R⁹ = H;
20 R^{10a} = -O-n-Butyl; R^{10b} = -H

25 Toluenesulfonic acid (0.256 g) was added to a stirred solution of rapamycin (1.13 g) in a solution of methylene chloride (20 mL) and n-butanol (20 mL) at 0 °C. After stirring at 0 °C for 2 hours, the reaction mixture was stirred at room temperature overnight. It was partitioned between ether and water. The organic phase was washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The product was purified by silica gel chromatography eluting with 40% acetone in hexanes to afford 0.41 g of the title compound. MS (FAB) *m/z*: M + K = 994.

30

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Example 78

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = OH;
R^{10a} = -O-n-Butyl; R^{10b} = H

5 The title compound is prepared from the compound resulting from Example 10, n-butanol and toluenesulfonic acid according to the procedure described in Example 77.

Example 79

10 Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = OH;
R^{10a} = -H; R^{10b} = OCH₃

15 The title compound is prepared from the compound resulting from Example 10, methanol and toluenesulfonic acid according to the procedure described in Example 77.

Example 80

20 Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = OH;
R^{10a} = -H; R^{10b} = H.

25 Triethylsilane (0.2 g) is added to a stirred solution of the compound resulting from Example 10 (1 g) and trifluoroacetic acid (1.2 g) in dichloromethane at -45 °C. After being stirred at that temperature for 1 hour, the reaction mixture is partitioned between ether and sodium bicarbonate. The organic phase is washed once with brine, dried over magnesium sulfate and solvent removed *in vacuo*. The product is purified by silica gel chromatography eluting with 40% acetone in hexanes.

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Example 81

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = OH; R^{10a} = -Allyl; R^{10b} = H

- 5 The title compound is prepared from the compound resulting from Example 10, allytrimethylsilane and trifluoroacetic acid according to the procedure described in Example 77.

Example 82

10 Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H; R⁹ = OH;
R^{10a} and R^{10b} taken together = O

- A solution of the compound resulting from Example 10 (1 g) and DDQ (2 equivalent) is stirred in wet dichloromethane at room temperature overnight.
 15 The product is purified by silica gel chromatography eluting with 40% acetone in hexanes.

Example 83

Alternate Preparation of

20 Formula IVb: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R^{10a} = OCH₃;
R^{10b} = H; R⁸ = R¹⁸ = H, R⁹ and R¹⁹ taken together form a bond

- A solution of the compound resulting from Example 58 (1 g) in chloroform is stirred at 50-60 °C for 4 hours. The product is purified by silica gel chromatography eluting with 40% acetone in hexanes.
 25

Example 84

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -O-C(O)-CH₃;

- The compound resulting from Example 1 is treated with acetic acid and Hünig's base in methylene chloride to afford the title compound.

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Example 85

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -O-C(O)-phenyl;

5 The compound resulting from Example 1 is treated with benzoic acid and Hünig's base in methylene chloride to afford the title compound.

Example 86

10 Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -O-C(O)-(4-pyridyl);

 The compound resulting from Example 1 is treated with isonicotinic acid and Hünig's base in methylene chloride to afford the title compound.

15 Example 87

Formula I: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -O-C(O)-N(OCH₃)(CH₃);

20 The title compound is prepared from the compound resulting from Example 11 and N,O-dimethylhydroxylamine according to the procedures described in Example 3.

Example 88

25 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -NH-C(O)-phenyl;

30 The title compound is prepared from the compound resulting from Example 51 and benzoyl chloride in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 52.

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Example 89

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -NH-C(O)-CH₂-CO₂H;

5 The title compound is prepared from the compound resulting from Example 51 and malonyl chloride in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 52.

Example 90

10 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -NH-C(O)-(CH₂)₂-CO₂H;

15 The title compound is prepared from the compound resulting from Example 51 and succinic anhydride in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 52.

Example 91

20 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -NH-C(O)-(CH₂)₃-CO₂H;

25 The title compound is prepared from the compound resulting from Example 51 and glutaric anhydride in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 52.

Example 92

30 Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -NH-C(O)-(CH₂)₄-CO₂H;

35 The title compound is prepared from the compound resulting from Example 51 and adipoyl chloride in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 52.

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Example 93

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = ethylene ketal of pyridin-2-on-1-yl;

5 The title compound is prepared from the compound resulting from Example 1 and 2-(2'-hydroxyethoxy)pyridine in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 72.

10

Example 94

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = ethylene ketal of piperidin-4-on-1-yl

15 The title compound is prepared from the compound resulting from Example 1 and the ethylene ketal of piperidin-4-one in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 72.

20

Example 95

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -(piperidin-4-ol-1-yl)

25 The title compound is prepared from the compound resulting from Example 1 and 4-hydroxypiperidine in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 72.

30

Example 96

Formula III: R¹ = methyl; R² = H; R³ = OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸ = H;
R⁹ = -(piperidin-4-on-1-yl)

 The title compound is prepared from the compound resulting from Example 1 and piperidin-4-one in the presence of N-methylmorpholine in dichloromethane according to the procedure described in Example 72.

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Example 97

Formula III: R¹= methyl; R²= H; R³= OH; R⁴ and R⁵ taken together = O;
R⁶ and R⁷ taken together = O; X and Y taken together = O; R⁸= H;
R⁹= -(piperidin-2-on-1-yl)

5 The title compound is prepared from the compound resulting from
 Example 72 by catalytic hydrogenation in ethanol using a palladium on carbon
 catalyst.

Example 98

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)OC₂H₅

15 A solution of rapamycin (304 mg, 0.33 mmol) and ethyl iodoacetate (276 µL, 2.33 mmol) in acetonitrile (300 µL) at 0 °C was treated with Ag₂O (308 mg, 1.33 mmol) in small portions over 5 minutes. The reaction was then warmed to ambient temperature and stirred for 5 days. The mixture was adsorbed onto silica gel by dilution of the mixture with CH₂Cl₂ (5 mL) followed by addition of silica gel (70-230 mesh, 60 A, 5mL) and solvent evaporation. The adsorbed silica bed was placed on a fresh pad of silica and eluted with mixtures of
 20 CH₂Cl₂:CH₃CN (9:1, 4:1, 2:1, 1:1). Fractions containing product were pooled, concentrated and further purified by HPLC on YMC 15 micron spherical 60A silica, eluting with a mixture of 3:1 hexane:acetone to provide desired product (112 mg). MS (FAB) *m/z*: M+K = 1038. Anal. calc'd. for C₅₅H₈₅NO₁₅: C, 66.04; H, 8.56; N, 1.40. Found: C, 65.83; H, 8.51; N, 1.36.

25

Example 99

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O; R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)OCH₂Ph(4-OMe)

30 The title compound is prepared using the procedure of Example 98 substituting p-methoxy-benzyl iodoacetate for ethyl iodoacetate.

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Example 100

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)OH.

The resultant product of Example 99 is treated with
 5 dichlorodicyanobenzoquinone in warm benzene. The mixture is concentrated
 and purified by chromatography on silica gel to provide pure title compound.

Example 101

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O; R⁶ and
 10 R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)NR²⁴R²⁵;
R²⁴= OCH₃; R²⁵=benzyl

The resultant product of Example 100 (912 mg, 0.94 mmol) is dissolved
 in THF (3 mL) and cooled to 0 °C before adding N-methylmorpholine (103.4
 µL, 0.94 mmol) followed by isobutyl chloroformate (122.2 µL, 0.94 mmol). The
 15 resulting suspension is stirred for 20 minutes at 0 °C after which time
 N-benzyl,O-methyl-hydroxylamine (257 mg, 1.88 mmol) is added, and stirring is
 continued overnight. The reaction mixture is purified by chromatography on
 silica gel to provide the title compound.

20

Example 102

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴= CH₃; R²⁵=O-benzyl

25 The title compound is prepared using the procedure of Example 101 and
 substituting N-methyl-O-benzyl-hydroxylamine for N-benzyl-O-methyl-
 hydroxylamine.

Example 103

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NHOCH₃

The title compound is prepared using the procedure of Example 101 and
 substituting O-methyl-hydroxylamine for N-benzyl-O-methyl-hydroxylamine.

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Example 104

5 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O; R⁶ and R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=OCH₃; R²⁵=CH₃

The title compound is prepared using the procedure of Example 101 and substituting N-methyl-O-methyl-hydroxylamine for N-benzyl-O-methyl-hydroxylamine.

10 Example 105

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O; R⁶ and R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=cyclopropyl

15 The title compound is prepared using the procedure of Example 101 and substituting cyclopropylamine for N-benzyl-O-methyl-hydroxylamine.

Example 106

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O; R⁶ and R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=OCH₃; R²⁵=cyclopropyl

The title compound is prepared using the procedure of Example 101 and substituting N-cyclopropyl-O-methyl-hydroxylamine for N-benzyl-O-methyl-hydroxylamine.

25 Example 107

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O; R⁶ and R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=OCH₃; R²⁵=cyclohexyl

30 The title compound is prepared using the procedure of Example 101 and substituting N-cyclohexyl-O-methyl-hydroxylamine for N-benzyl-O-methyl-hydroxylamine.

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Example 108

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=OCH₃; R²⁵= -CH₂CH₂OH.

5 The title compound is prepared using the procedure of Example 101 and substituting N-(2-hydroxyethyl)-O-methyl-hydroxylamine for N-benzyl-O-methyl-hydroxylamine.

Example 109

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= -CH₂CO₂CH₂Ph(4-OMe).

15 The title compound is prepared using the procedure of Example 101 and substituting glycine p-methoxybenzyl ester for N-benzyl-O-methyl-hydroxylamine.

Example 110

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= -CH₂CO₂H

25 The title compound is prepared by the procedure described in Example 100 substituting the product from Example 109 for the product from Example 99.

Example 111

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=3-biphenyl

35 The title compound is prepared using the procedure of Example 101 and substituting 3-biphenylamine for N-benzyl-O-methyl-hydroxylamine.

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Example 112

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=-CH₂CH₂OH; R²⁵= 3-biphenyl

5 The title compound is prepared using the procedure of Example 101 and substituting N,N-(ethanol-2-yl)-(3-biphenyl)-amine for N-benzyl-O-methyl-hydroxylamine.

Example 113

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=-CH₂CH₂N(CH₃)(CH₂CH₂OH); R²⁵= phenyl

15 The title compound is prepared using the procedure of Example 101 and substituting N-phenyl-N'-methyl-N'-(ethanol-2-yl)-ethyldiamine for N-benzyl-O-methyl-hydroxylamine.

Example 114

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=-CH₂CH₂N(CH₃)₂; R²⁵= phenyl

25 The title compound is prepared using the procedure of Example 101 and substituting N-phenyl-N',N'-dimethyl-ethyldiamine for N-benzyl-O-methyl-hydroxylamine.

Example 115

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=CH₂(3-pyridyl); R²⁵= CH₂(3-pyridyl)

35 The title compound is prepared using the procedure of Example 101 and substituting 3,3'-dipicolylamine for N-benzyl-O-methyl-hydroxylamine.

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Example 116

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NH-(4-morpholinyl)

5 The compound resulting from Example 100 is activated as in Example 101 and then treated with 1 equivalent of 4-aminomorpholine and 0.1 equivalents of 4-dimethylaminopyridine instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

10

Example 117

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; where R²⁴ and R²⁵ taken together=
-CH₂CH₂SCH₂CH₂-, thus forming a six membered ring incorporating the
15 nitrogen to which they are attached

15

The compound resulting from Example 100 is activated as in Example 101 and then treated with thiomorpholine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

20

Example 118

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 4-CF₃-phenyl

25

The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-aminobenzotrifluoride instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

30

Example 119

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=4-F-phenyl

The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-fluoroaniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

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Example 120

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
5 R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 4-(4-morpholino)-phenyl

The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-morpholinoaniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

10

Example 121

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
10 R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 4-HO-phenyl

The compound resulting from Example 100 is activated as in Example 15 101 and then treated with *p*-aminophenol instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

20

Example 122

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
20 R⁶ and R⁷ taken together=O; X and Y taken together=O;
 R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 3-pyridyl

The compound resulting from Example 100 is activated as in Example 101 and then treated with 3-aminopyridine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

25

Example 123

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
30 R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 4-pyridyl

The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-aminopyridine instead of N-benzyl,O-methyl-hydroxylamine to give the title compound.

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Example 124

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 2-pyridyl

5 The compound resulting from Example 100 is activated as in Example 101 and then treated with 2-aminopyridine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 125

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= NHCO₂CH₃

15 The compound resulting from Example 100 is activated as in Example 101 and then treated with methylcarbazate instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 126

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-(L-prolinecarboxamide)

25 The compound resulting from Example 100 is activated as in Example 101 and then treated with L-prolinecarboxamide instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

Example 127

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-(D-prolinecarboxamide)

35 The compound resulting from Example 100 is activated as in Example 101 and then treated with D-Prolinecarboxamide instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

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Example 128

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-(L-prolinol).

- 5 The compound resulting from Example 100 is activated as in Example
 101 and then treated with L-prolinol instead of N-benzyl-O-methyl-
 hydroxylamineto give the title compound.

Example 129

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-(D-prolinol)

- 15 The compound resulting from Example 100 is activated as in Example
 101 and then treated with D-prolinol instead of N-benzyl-O-methyl-
 hydroxylamineto give the title compound.

Example 130

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)N(CH₂CH₂OH)NH(CO₂CH₃)

- The compound resulting from Example 100 is activated as in Example
 101 and then treated with N-(ethanol-2-yl)-N'-carbomethoxy-hydrazine instead
 of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 131

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 3-(phenylethynyl)phenyl

- 25 The compound resulting from Example 100 is activated as in Example
 101 and then treated with 3-phenylethynylaniline instead of N-benzyl-O-methyl-
 hydroxylamineto give the title compound.

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Example 132

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=CH₂CH₂CH₂OH; R²⁵=4-fluorophenyl

5 The compound resulting from Example 100 is activated as in Example 101 and then treated with (4-fluoroanilino)-1-propanol instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

Example 133

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=CH₂CH₂CH₂OCOCH₂CH₂CO₂H;
R²⁵=4-fluorophenyl.

15 The compound resulting from Example 132 is treated with succinic anhydride, by the procedure described in Tetrahedron Letters, 30: 5045-48 (1989), to give the title compound.

Example 134

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵, R²⁴ and R²⁵ are taken together as the following diradical, -CH₂CH₂C(OCH₂CH₂O)CH₂CH₂-

25 The compound resulting from Example 100 is activated as in Example 101 and then treated with 1,4-dioxa-8-azaspiro[4.5]decane instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

Example 135

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)HNHN-CO-(4-pyridyl)

The compound resulting from Example 100 is activated as in Example 101 and then treated with isonicotinic acid hydrazide instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

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Example 136

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=3-fluorophenyl

- 5 The compound resulting from Example 100 is activated as in Example 101 and then treated with *m*-fluoroaniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 137

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 3-hydroxy-phenyl

- 15 The compound resulting from Example 100 is activated as in Example 101 and then treated with *m*-aminophenol instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

Example 138

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵, R²⁴ and R²⁵ are taken together as the following diradical: -CH₂CH₂-N(CH₃)-CH₂CH₂-.

- 25 The compound resulting from Example 100 is activated as in Example 101 and then treated with N-methylpiperazine instead of N-benzyl-O-methyl-hydroxylaminet o give the title compound.

Example 139

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 1,4-benzodioxan-6-yl

- 30 The compound resulting from Example 100 is activated as in Example 101 and then treated with 1,4-benzodioxan-6-amine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

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Example 140

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 1,3-benzodioxol-5-yl

5 The compound resulting from Example 100 is activated as in Example 101 and then treated with 3,4-(methylenedioxy)-aniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 141

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= 1-naphthalenyl

15 The compound resulting from Example 100 is activated as in Example 101 and then treated with 1-naphthylamine instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

Example 142

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-(1-pyrrolidinyl)

25 The compound resulting from Example 100 is activated as in Example 101 and then treated with pyrrolidine instead of N-benzyl-O-methyl-hydroxylamine to provide the title compound.

Example 143

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-(1-piperidinyl)

35 The compound resulting from Example 100 is activated as in Example 101 and then treated with piperidine instead of N-benzyl-O-methyl-hydroxylamine to provide the title compound.

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Example 144

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)OCH₂-(9-fluorenyl)

- 5 Rapamycin (11.0 g, .012 mol) is dissolved in distilled CH₂Cl₂ (50 mL). Rhodium (II) acetate dimer (100 mg) is added and the mixture cooled to 0 °C. 9-Fluorenylmethyl diazoacetate (3.35 g, .012 mol) is dissolved in CH₂Cl₂ (10 mL) and the solution added to the reaction via syringe pump at a rate of approximately 0.5 mL/hour. Addition is complete in approximately 24 hours.
- 10 The reaction is stirred at 0 °C for an additional 24 hours then loaded onto silica (230-400 mesh, 400 g) and the solvent evaporated by airflow in the hood. The adsorbed silica is layered over fresh silica (800 g) in a 1 L fritted glass funnel and eluted with mixtures of CH₂Cl₂ and CH₃CN. Fractions containing product are combined and concentrated to provide title compound.

15

Example 145

Alternate Preparation of

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O; R⁸= -OCH₂C(O)OH

- 20 The resultant product of Example 144 is dissolved in CH₂Cl₂, whereupon piperidine is added. The solution is stirred at room temperature for 2 hours then transferred to a separatory funnel, diluted with additional CH₂Cl₂ (100 mL), then washed with 1 N HCl (2 x 100 mL) and brine (2 x 100 mL). The organic layer is dried (Na₂SO₄), filtered, and the solvent removed *in vacuo* to give crude title
- 25 compound which is purified by chromatography on silica gel.

Example 146

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵= -CH₂CH₂C₆H₅

- 30 The compound resulting from Example 145 is dissolved in dichloromethane and the solution cooled to 0 °C. HOBT · H₂O is added followed by EDAC then phenethylamine. The reaction is warmed to room temperature and stirred overnight. Dichloromethane is added and the organic phase washed

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with 1 N HCl, saturated sodium bicarbonate solution, and then brine. The organic layer is dried (Na_2SO_4), filtered, and solvent removed *in vacuo* to give crude product. This is purified by HPLC (20 x 300 mm silica column) eluting with 3:1 hexane-acetone. Fractions containing product are combined and solvent removed *in vacuo* to give the title compound.

Example 147

10 Formula VII: $\text{R}^1=\text{CH}_3$; $\text{R}^2=\text{R}^9=\text{H}$; $\text{R}^3=\text{OH}$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
 $\text{R}^8=-\text{OCH}_2\text{C}(\text{O})\text{NR}^{24}\text{R}^{25}$; $\text{R}^{24}=\text{OCH}_3$; $\text{R}^{25}=-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$

The title compound is prepared using the procedures described in Example 146 and substituting N,N-methoxy, 2-phenylethyl amine for 2-phenylethylamine.

15 Example 148

10 Formula VII: $\text{R}^1=\text{CH}_3$; $\text{R}^2=\text{R}^9=\text{H}$; $\text{R}^3=\text{OH}$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
 $\text{R}^8=-\text{OCH}_2\text{C}(\text{O})\text{NH}(\text{CH}_2)_5\text{NH-dansyl}$

20 The title compound is prepared using the procedures described in Example 146 and substituting dansyl cadaverine for 2-phenylethylamine.

Example 149

25 Formula VII: $\text{R}^1=\text{CH}_3$; $\text{R}^2=\text{R}^9=\text{H}$; $\text{R}^3=\text{OH}$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
 $\text{R}^8=-\text{OCH}_2\text{C}(\text{O})\text{NR}^{24}\text{R}^{25}$; $\text{R}^{24}=\text{H}$; $\text{R}^{25}=-\text{C}_6\text{H}_5$

The title compound is prepared using the procedures described in Example 146 and substituting aniline for 2-phenylethylamine.

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Example 150

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NH(CH₂)₂N(CH₂CH₂)₂O

5 The title compound is synthesized in the manner described for Example
 101 substituting 2-(4-morpholino)-ethylamine for N-benzyl-O-methyl-
 hydroxylamine.

Example 151

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NH(CH₂)₃N(CH₂CH₂)₂O

15 The title compound is prepared using the procedures described in
 Example 146 and substituting 3-(4-morpholino)-propylamine for 2-
 phenylethylamine.

Example 152

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NH(CH₂)₂N(CH₃)₂

25 The title compound is synthesized in the manner described for Example
 101 substituting 2-dimethylamino-ethylamine for N-benzyl-O-methyl-
 hydroxylamine.

25

Example 153

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=-(CH₂)₃N(CH₃)₂

35 The title compound is prepared using the procedures described in
 Example 146 and substituting 3-dimethylamino-propylamine for 2-
 phenylethylamine.

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Example 154

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-[S)-HNCH(CH₂C₆H₅)CO₂CH₂Ph(4-OMe)]

5 The title compound is prepared using the procedures described in Example 146 and substituting L-phenylalanine p-methoxybenzylester for 2-phenylethylamine.

10

Example 155

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-[S)-HNCH(CH₂C₆H₅)CO₂H]

15 The title compound is synthesized in the manner described in Example 100 substituting the product from Example 154 for the product from Example 99.

20

Example 156

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-[R)-HNCH(CH₂C₆H₅)CO₂CH₂Ph(4-OMe)]

25 The title compound is synthesized in the manner described for Example 146 substituting D-phenylalanine p-methoxybenzylester for 2-phenylethylamine.

30

Example 157

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)-[R)-HNCH(CH₂C₆H₅)CO₂H]

35 The title compound is synthesized in the manner described in Example 100 substituting the product from Example 156 for the product from Example 99.

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Example 158

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;

R⁶ and R⁷ taken together=O; X and Y taken together=O;

5 R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=-(CH₂)₂SH

The product of Example 100 (1.4 g, 1.4 mmol) is dissolved in THF (4.5 mL) and the solution cooled to 0 °C before adding N-methylmorpholine (155.1 μL, 1.4 mmol) followed by isobutyl chloroformate (122.2 μL, 1.4 nmol). The resulting suspension is stirred for 20 minutes at 0 °C then 2-aminoethanethiol hydrochloride (320.8 mg, 2.8 mmol) is added. The mixture is stirred for 3 hours at room temperature before addition of more N-methylmorpholine (387.8 μL, 3.5 mmol). The reaction is stirred overnight, loaded onto silica (40 mL) in a fritted funnel, then eluted with dichloromethane (100 mL), 1:1 hexane/acetone (200 mL), followed by acetone (100 mL). Fractions containing product are combined and solvent removed *in vacuo* to give crude product. This material is further purified by HPLC (30 x 300 mm silica column) eluting with 2:1 hexane/acetone to provide the title compound.

Example 159

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;

R⁶ and R⁷ taken together=O; X and Y taken together=O;

R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=-(CH₂)₃SH

The title compound is synthesized in the manner described for Example 158 substituting 3-amino-propanethiol for 2-aminoethanethiol.

25

Example 160

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;

30 R⁶ and R⁷ taken together=O; X and Y taken together=O;

R⁸= -OCH₂C(O)O(t-butyl)

Silver (I) oxide (926 mg, 4.0 mmol) is added to rapamycin (791 mg, 1.0 mmol) dissolved in acetonitrile (0.8 mL) and t-butyl iodoacetate (828 μL, 7.0 mmol). The mixture is stirred at room temperature for 5 days. volatiles are

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removed *in vacuo*. The product is isolated by chromatography on silica gel as described in Example 98.

Example 161

5 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=2-naphthyl

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with 2-naphthylamine instead of N-10 benzyl-O-methyl-hydroxylamine to give the title compound.

Example 162

15 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=4-(H₂NSO₂)phenyl

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with sulfanilamide instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

20 Example 163

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)-(4-(2-hydroxyethyl)piperzin-1-yl)

25 The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with N-(2-hydroxyethyl)-piperazine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 164

30 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=CH₃; R²⁵=phenyl

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with N-methylaniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

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Example 165

5 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=R²⁵=-CH₂CH₂OH

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with N,N-bis-(2-hydroxyethyl)-amine instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

10

Example 166

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=CH₃; R²⁵=-CH₂CH₂CH₂N(CH₃)₂

15

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with N,N'-methyl-(3-dimethylaminopropyl)-amine instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

20

Example 167

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=phenyl; R²⁵=-CH₂CH₂CH₂OH

25

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with N,N-phenyl-(3-hydroxypropyl)-amine instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

30

Example 168

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=-CH(CH₂OH)₂

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with serinol instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

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Example 169

Formula VII: $R^1=CH_3$; $R^2=R^9=H$; $R^3=OH$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
5 $R^8= -OCH_2C(O)NR^{24}R^{25}$; $R^{24}=H$; $R^{25}= 3-(CF_3)-phenyl$

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with 3-trifluoromethylaniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

10

Example 170

Formula VII: $R^1=CH_3$; $R^2=R^9=H$; $R^3=OH$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
 $R^8= -OCH_2C(O)NR^{24}R^{25}$; $R^{24}-R^{25}= -CH_2CN$

15

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with iminodiacetonitrile instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

20

Example 171

Formula VII: $R^1=CH_3$; $R^2=R^9=H$; $R^3=OH$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
 $R^8= -OCH_2C(O)-(1-aziridinyl)$

25

The compound resulting from Example 100 is activated by the procedure described in Example 101 and then treated with aziridine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

30

Example 172

Formula VII: $R^1=CH_3$; $R^2=R^9=H$; $R^3=OH$; R^4 and R^5 taken together=O;
 R^6 and R^7 taken together=O; X and Y taken together=O;
 $R^8= -OCH_2NHC(O)-(4-morpholinyl)$

The compound resulting from Example 100 (564 mg, 0.58 mmol) in THF (6 mL) is stirred together with N-methylpiperidine (73 μ L, 0.58 mmol) and diphenylphosphorylazide (73 μ L, 0.58 mmol) at ambient temperature for 5

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minutes, then at reflux for 3 hours. The stirring solution is cooled to ambient temperature and treated with morpholine (157 μ L, 1.8 mmol). The mixture is purified by HPLC on a column 20 x 300 mm (YMC 15u, 60 \AA spherical SiO_2) eluting with a step gradient of hexane:acetone (1:1) then hexane:acetone (2:3), to provide title compound.

Example 173

Formula VII: R¹=CH₃; R²=R⁹-H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂NHC(O)NR²⁴R²⁵, R²⁴=H; R²⁵=phenyl

The compound resulting from Example 100 is activated as in Example 172 and then treated with aniline instead of morpholine to give the title compound.

Example 174

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂NHC(O)-phenyl

The compound resulting from Example 100 is activated as in Example 172 and then treated with benzoic acid instead of morpholine, whereupon the mixture is heated. Purification by chromatography on silica gel provides the title compound.

Example 175

25 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂NHC(O)NR²⁴R²⁵; R²⁴=H; R²⁵=-CH₂CH₂CH₂OH

The compound resulting from Example 100 is activated as in Example 172 and then treated with 3-aminopropanol instead of morpholine to give the title compound.

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Example 176

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H;
R²⁵= 6-carbomethoxymethylmercaptopurine hydrazid-yl

5

The compound resulting from Example 100 is activated as in Example 101 and then treated with 6-carbomethoxymethylmercaptopurine hydrazide instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

10

Example 177

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵, R²⁴ and R²⁵ are taken together as the following diradical: -CH₂CH₂SO₂CH₂CH₂-

15

The compound resulting from Example 100 is activated as in Example 101 and then treated with thiomorpholine sulfone instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

20

Example 178

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=CH₂CH₂-(4-F-phenyl)

25

The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-fluorophenethylamine instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

30

Example 179

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=4-Cl-phenyl

The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-chloroaniline instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

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Example 180

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=4-(OCH₃)-phenyl

5 The compound resulting from Example 100 is activated as in Example 101 and then treated with 4-methoxyaniline instead of N-benzyl-O-methyl-hydroxylamine to give the title compound.

Example 181

10 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=H; R²⁵=3-I-phenyl

15 The compound resulting from Example 100 is activated as in Example 101 and then treated with 3-iodoaniline instead of N-benzyl-O-methyl-hydroxylamineto give the title compound.

Example 182

20 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸=-OCH₂C(O)O-CH₂-[(1R)-(+)-alpha-pinene-10-yl])

25 (a) A three-neck 2 L roundbottom flask equipped with an overhead stirrer was charged with diethylether (800 mL), chloroacetyl chloride (40 mL, 0.5 mol) and (1R)-(-)-nopol (85.3 mL, 0.5 mol). At 0 °C, triethylamine (69.5 mL, 0.5 mol) was added dropwise over 15 minutes. After stirring at 0 °C for 1 hour, the mixture was warmed to ambient temperature and stirred for 18 hours. The mixture was vacuum filtered through a Buchner funnel and the white cake was extracted with ether (2 x 200 mL). The filtrates were then washed sequentially with 0.5 N HCl (500 mL), water (500 mL) and brine (500 mL). After drying the organics (Na₂SO₄), the mixture was filtered and concentrated to a pale tan oil (104 g). The resultant nopol chloroacetate was sufficiently pure to carry forward in the next step.

30 (b) Sodium Iodide (20.1 g, 134 mmol) was refluxed in acetone (55 mL) for 5 minutes and cooled to room temperature. Nopol chloroacetate from step (a) (5.85 g, 24.17 mmol) was added, and the reaction was stirred for 30 minutes.

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The solvent was removed *in vacuo*, and the resulting slurry was partitioned between water (30 mL) and ethyl acetate (20 mL). The aqueous portion was extracted with additional ethyl acetate (20 mL). The combined organics were washed sequentially with saturated sodium bicarbonate (30 mL) and 10% sodium bisulfite (30 mL), dried (sodium sulfate) and concentrated *in vacuo* to an amber oil (7 g). The resulting nopol iodoacetate was sufficiently pure to use in the next step.

(c) Rapamycin (2.9 g, 3.16 mmol) and nopol iodoacetate from step (b) (5.70 g, 17.1 mmol, 5.4 eq) are dissolved in acetonitrile (1.5 mL). After a homogeneous solution is obtained, it is cooled to 0 °C and silver(I) oxide (3.13 g, 13.4 mmol) is added portionwise (15 minutes). The solution is brought to room temperature by gradual melting of the ice and is stirred for 5 days. The reaction is diluted in diethyl ether and poured onto silica gel (70-230 mesh, 20 mL) and allowed to air dry. The adsorbed silica is layered on fresh silica (70-230 mesh, 100 mL) and eluted with methylene chloride (150 mL); methylene chloride:acetonitrile (9:1, 450 mL); (3:1, 300 mL); (1:1, 200 mL); acetone (200 mL). 50 mL fractions are collected. Fractions containing product are pooled, concentrated, further purification by HPLC on silica eluting with 3:1 hexane:acetone provides pure title compound.

20

Example 183

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)O-CH₂-[4-nitrophenyl]

25 (a) A three-neck 2 L roundbottom flask equipped with an overhead stirrer was charged with diethylether (800 mL), chloroacetyl chloride (40 mL, 0.5 mol) and 4-nitrobenzylalcohol (76.5 g, 0.5 mol) and cooled to 0 °C. Triethylamine (69.5 mL, 0.5 mol) was added dropwise over 15 minutes. After stirring at 0 °C for 1 hour, the mixture was warmed to ambient temperature and stirred for 18 hours. The mixture was vacuum filtered through a Buchner funnel and the white cake was extracted with ether (2 x 200 mL). The filtrates were then washed sequentially with 0.5 N HCl (500 mL), water (500 mL) and brine (500 mL). After drying the organics (Na₂SO₄), the mixture was filtered and concentrated to

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a pale tan solid (74.8 g). The crude product was recrystallized from diethylether. m.p. 71-72 °C.

(b) Sodium Iodide (39.5 g, 260 mmol) was refluxed in acetone (104 mL) for 3 minutes and cooled to room temperature. 4-Nitrobenzyl chloroacetate from step (a) (10.7 g, 47 mmol) was added, and the reaction was stirred for 30 minutes. The solvent was removed *in vacuo*, and the resulting slurry was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with additional ethyl acetate (50 mL), and the combined organics were washed sequentially with saturated sodium bisulfite (2 x 50 mL) and brine (50 mL). The organics were dried (sodium sulfate) and concentrated *in vacuo* to pure product (15.6 g).

(c) Rapamycin (5.8 g, 6.3 mmol) and 4-nitrobenzyl iodoacetate from step (b) (15.6 g, 48.6 mmol, 7.7 eq) are dissolved in acetonitrile (2.5 mL). After a homogeneous solution is obtained, it is cooled to 0 °C and silver(I) oxide (5.9 g, 25.6 mmol) is added portionwise (15 minutes). The solution is brought to room temperature by gradual melting of the ice and is stirred for 5 days. The reaction is diluted in diethyl ether (25 mL), poured onto silica gel (70-230 mesh, 40 mL) and allowed to air dry. The adsorbed silica is layered on fresh silica (70-230 mesh, 200 mL) and eluted with methylene chloride (500 mL); methylene chloride:acetonitrile (9:1, 400 mL); (6:1, 300 mL); (3:1, 1000 mL); (1:1, 500 mL); (1:2, 300 mL). 100 mL fractions are collected. Fractions containing desired product ($\text{CH}_2\text{Cl}_2:\text{CH}_3\text{CN}$ 3:1) are pooled and concentrated *in vacuo* to provide the title compound.

25

Example 184

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;

R⁶ and R⁷ taken together=O; X and Y taken together=O;

R⁸=-OCH₂C(O)NR²⁴R²⁵; R²⁴=-(CH₂)₂N(CH₂CH₂)₂O; R²⁵=-CH₂CH₂OH

The title compound is synthesized by the procedures described in Example 101 substituting N,N-[2-hydroxyethyl][2-(4-morpholino)-ethyl]amine for N-benzyl-O-methyl-hydroxylamine.

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Example 185

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyloxy

5 Alpha-D-glucopyranosyl bromide tetraacetate (2.46 g, 6 mmol) and rapamycin (913 mg, 1.0 mmol) in acetonitrile (1 mL) at 0 °C is treated with Ag₂O (928 mg, 4 mmol). The mixture is warmed to ambient temperature and stirred for 5 days. Purification of the mixture by chromatography on silica gel provides the title product.

10

Example 186

Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyloxy

15 Alpha-D-glucopyranosyl bromide tetraacetate (1.23 g, 3 mmol), rapamycin (913 mg, 1.0 mmol) and crushed 4Å molecular sieves (2 g) in anhydrous methylene chloride (150 mL) at -78 °C is treated with AgCO₃ (1.7 g, 10 mmol) followed by Ag(OSO₂CF₃) (257 mg, 1.0 mmol). The mixture is warmed to ambient temperature over 8 hours and is stirred for an additional 5 hours. Purification of the mixture by chromatography on silica gel provides title product.

20

Example 187

25 Formula VII: R¹=CH₃; R²=R⁹=H; R³=OH; R⁴ and R⁵ taken together=O;
R⁶ and R⁷ taken together=O; X and Y taken together=O;
R⁸= -OCH₂C(O)OCH₂CCl₃

The title compound is prepared using the procedures described in Example 183 substituting 2,2,2-trichloroethanol for p-nitrobenzylalcohol.

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Example 188

In vitro Assay of Biological Activity

The immunosuppressant activity of the compounds of the present invention was determined using the human mixed lymphocyte reaction (MLR) assay described by Kino, T. *et al.* in *Transplantation Proceedings*, XIX(5):36-39, Suppl. 6 (1987). The *in vitro* immunosuppressant activity of the compounds of the present invention was determined in a one way allogeneic mixed leukocyte response (MLR) assay using rat lymph node and spleen cells, conducted as follows: Responder cells were obtained from the lymph nodes of Brown Norway rats (Harlan Sprague Dawley, Inc., Indianapolis, IN) and the stimulator cells were isolated from the spleens of Lewis rats (Harlan Sprague Dawley, Inc., Indianapolis, IN). 200-250 gram rats were sacrificed by asphyxiation with CO₂ and the popliteal and mesenteric lymph nodes or spleen were removed by sterile dissection. The tissue was placed in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 50 µM 2-mercaptoethanol, 50 units/mL penicillin G, and 50 µg/mL streptomycin (complete RPMI medium). After mechanically disrupting the tissue and allowing debris to settle at 1 x g, the suspended cells were aspirated. The cell suspensions were centrifuged 10 min at 400 x g and the responder cells resuspended in complete RPMI medium at 2 x 10⁶ cells/mL. To remove red cells, the spleen cells were suspended in 0.14 M NH₄Cl/0.017 M Tris-HCl lysing buffer, pH 7.4, for 2 minutes, mixed with RPMI 1640, and centrifuged as before. The spleen cells were subsequently washed three times by centrifugation in RPMI 1640. To inhibit their ability to proliferate, spleen cells were suspended at 1 x 10⁷ cells/mL in complete RPMI medium and incubated in the presence of 25 µg/mL of mitomycin C for 30 minutes at 37 °C. The mitomycin C-treated spleen cells were washed three times by centrifugation in RPMI 1640 before being suspended in complete RPMI medium at 4 x 10⁶ cells/mL.

For the MLR, 1 x 10⁵ lymph node cells were mixed with 5 x 10⁵ mitomycin C-treated spleen cells in 0.2 mL of complete RPMI 1640 and cultured in 95% air / 5% CO₂ atmosphere for 120 hours at 37 °C. Test compounds were dissolved at 10 mM in dimethylsulfoxide, diluted in complete RPMI medium, and 25 µL of the test compound was added to the lymph node cells before addition of the spleen cells. During the final 6 hours, the cells were labeled with

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0.5 μ Ci per well of tritiated thymidine (3 H-TdR; DuPont NEN Research Products, Boston, MA). The cells were harvested by vacuum filtration onto glass fiber filters and the filter radioactivity measured with a MATRIX 9600 direct beta counter (Packard Instrument Company, Meriden, CT). To calculate
5 the compound concentration which caused 50% inhibition (IC₅₀) in an assay, the inhibition data was fit to a log-logistic linear function.

The results of the assay, shown below in Table 1, demonstrate that the compounds tested are effective immunomodulators at nanomolar concentrations.

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Table 1

Mixed Leukocyte Response (MLR)

<u>Example</u>	<u>Rat MLR IC₅₀ (nM)</u>
3	0.13
10	0.03
17	0.15
38	0.03
50	0.96
39	0.14
71	0.12
72	0.99
74	1.81

5 The compounds of the invention, including but not limited to those specified in the examples, possess immunomodulatory activity in mammals (especially humans). As immunosuppressants, the compounds of the present invention are useful for the treatment and prevention of immune-mediated diseases such as the resistance by transplantation of organs or tissue such as
10 heart, kidney, liver, medulla ossium, skin, cornea, lung, pancreas, intestinum tenue, limb, muscle, nervus, duodenum, small-bowel, pancreatic-islet-cell, etc.; graft-versus-host diseases brought about by medulla ossium transplantation; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes
15 uveitis, allergic encephalomyelitis, glomerulonephritis, and the like; and further infectious diseases caused by pathogenic microorganisms, such as HIV. In the particular cases of HIV-1, HIV-2 and related retroviral strains, inhibition of T-cell proliferation will suppress the replication of the virus, since the virus relies upon the T-cell's proliferative functions to replicate. Further uses include the
20 treatment and prophylaxis of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous

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pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne and Alopecia areata; various eye diseases (autoimmune and otherwise) such as keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, Scleritis, Graves' ophthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, etc.; reversible obstructive airway disease, which includes conditions such as asthma (for example, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (for example, late asthma and airway hyper-responsiveness), bronchitis and the like; inflammation of mucosa and blood vessels such as gastric ulcers, vascular damage caused by ischemic diseases and thrombosis. Moreover, hyperproliferative vascular diseases such as intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion, particularly following biologically or mechanically mediated vascular injury could be treated or prevented by the compounds of the invention. Other treatable conditions include but are not limited to ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns and leukotriene B₄-mediated diseases; intestinal inflammations/allergies such as Coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis; food-related allergic diseases which have symptomatic manifestation remote from the gastrointestinal tract (e.g. migraine, rhinitis and eczema); renal diseases such as interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy; nervous diseases such as multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis and radiculopathy; endocrine diseases such as hyperthyroidism and Basedow's disease; hematologic diseases such as pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia and anerythroplasia; bone diseases such as osteoporosis; respiratory diseases such as sarcoidosis, fibroid lung and idiopathic interstitial pneumonia; skin disease such as dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases such as

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arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis; collagen diseases such as scleroderma, Wegener's granuloma and Sjogren's syndrome; adiposis; eosinophilic fasciitis; periodontal disease such as lesions of gingiva, periodontium, alveolar bone and substantia ossea dentis;

5 nephrotic syndrome such as glomerulonephritis; male pattern aleopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth; muscular dystrophy; Pyoderma and Sezary's syndrome; Addison's disease; active oxygen-mediated diseases, as for example organ injury such as ischemia-reperfusion injury of organs (such as

10 heart, liver, kidney and digestive tract) which occurs upon preservation, transplantation or ischemic disease (for example, thrombosis and cardiac infarction); intestinal diseases such as endotoxin-shock; pseudomembranous colitis and colitis caused by drug or radiation; renal diseases such as ischemic acute renal insufficiency and chronic renal insufficiency; pulmonary diseases

15 such as toxinosis caused by lung-oxygen or drug (for example, paracort and bleomycins), lung cancer and pulmonary emphysema; ocular diseases such as cataracta, siderosis, retinitis, pigmentosa, senile macular degeneration, vitreal scarring and corneal alkali burn; dermatitis such as erythema multiforme, linear IgA ballous dermatitis and cement dermatitis; and others such as gingivitis,

20 periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (for example, air pollution), aging, carcinogenis, metastasis of carcinoma and hypobaropathy; diseases caused by histamine or leukotriene-C₄ release; Behcet's disease such as intestinal-, vasculo- or neuro-Behcet's disease, and also Behcet's which affects the oral cavity, skin, eye, vulva, articulation, epididymis, lung,

25 kidney and so on. Furthermore, the compounds of the invention are useful for the treatment and prevention of hepatic disease such as immunogenic diseases (for example, chronic autoimmune liver diseases such as autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxin, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis, cirrhosis (such as alcoholic cirrhosis) and hepatic failure such as fulminant hepatic failure, late-onset hepatic failure and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases), and moreover are useful for various diseases because of their useful activity such as

30

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augmentation of chemotherapeutic effect, cytomegalovirus infection, particularly HCMV infection, anti-inflammatory activity, and so on.

Additionally, compounds of the invention possess FK-506 antagonistic properties. The compounds of the present invention may thus be used in the treatment of immunodepression or a disorder involving immunodepression.

Examples of disorders involving immunodepression include AIDS, cancer, senile dementia, trauma (including wound healing, surgery and shock) chronic bacterial infection, and certain central nervous system disorders. The immunodepression to be treated may be caused by an overdose of an immunosuppressive macrocyclic compound, for example derivatives of 12-(2-cyclohexyl-1-methylvinyl)-13, 19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0 4,9]octacos-18-ene such as FK-506, or rapamycin. Overdosing of such medicants by patients is quite common upon their realizing that they have forgotten to take their medication at the prescribed time and can lead to serious side effects.

The ability of the compounds of the invention to treat proliferative diseases can be demonstrated according to the methods described in Bunchman ET and CA Brookshire, Transplantation Proceed. 23 967-968 (1991); Yamagishi, et al., Biochem. Biophys. Res. Comm. 191 840-846 (1993); and Shichiri, et al., J. Clin. Invest. 87 1867-1871 (1991). Proliferative diseases include smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels.

Aqueous liquid compositions of the present invention are particularly useful for the treatment and prevention of various diseases of the eye such as autoimmune diseases (including, for example, conical cornea, keratitis, dysophia epithelialis corneae, leukoma, Mooren's ulcer, scleritis and Graves' ophthalmopathy) and rejection of corneal transplantation.

30

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. Alternatively, the compound may be administered as a

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pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.001 to about 3 mg/kg/day. For purposes of oral administration, more preferable doses may be in the range of from about 0.005 to about 1.5 mg/kg/day. If desired, the effective daily dose may be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The pharmaceutical compositions of the present invention comprise a compound of the invention and a pharmaceutically acceptable carrier or excipient, which may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), buccally, or as an oral or nasal spray. The phrase "pharmaceutically acceptable carrier" means a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration

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which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, 5 dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures 10 thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, 15 wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable 20 pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or 25 amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

30 Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot

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injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the 5 form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier 10 such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca 15 starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, 20 sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

25 The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, 30 optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

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Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents,

5 solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

10 Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols,

15 polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Topical administration includes administration to the skin or mucosa, including surfaces of the lung and eye. Compositions for topical administration, including those for inhalation, may be prepared as a dry powder which may be pressurized or non-pressurized. In non-pressurized powder compositions, the active ingredient in finely divided form may be used in admixture with a larger-sized pharmaceutically acceptable inert carrier comprising particles having a size, for example, of up to 100 micrometers in diameter. Suitable inert carriers include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

Alternatively, the composition may be pressurized and contain a compressed gas, such as nitrogen or a liquified gas propellant. The liquified propellant medium and indeed the total composition is preferably such that the active ingredient does not dissolve therein to any substantial extent. The pressurized composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-ionic surface active agent or may be a

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solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of a sodium salt.

A further form of topical administration is to the eye, as for the treatment of immune-mediated conditions of the eye such as autoimmune diseases,
5 allergic or inflammatory conditions, and corneal transplants. The compound of the invention is delivered in a pharmaceutically acceptable ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, as for example the anterior chamber, posterior
10 chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may, for example, be an ointment, vegetable oil or an encapsulating material.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention
15 with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form
20 of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can
25 contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their

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equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, constituents, derivatives, intermediates, syntheses, formulations and/or methods
5 of use of the invention, may be made without departing from the spirit and scope thereof.

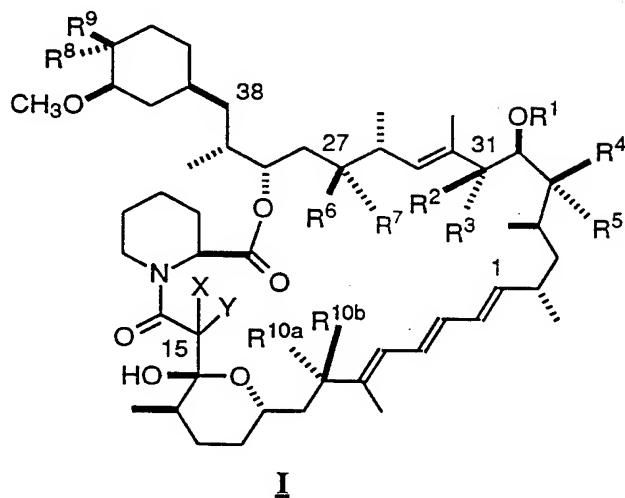
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CLAIMS

What is claimed is:

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1. A compound of the formula:



10 wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

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R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

20 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

(1) oxo,

(2) diazo,

25 (3) =CH₂

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- (4) -O-(CH₂)₂-O-,
- (5) -S-(CH₂)₂-S-,
- (6) -O-(CH₂)₃-O-,
- (7) -S-(CH₂)₃-S-,

30 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
35 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

40 R⁹ is

- (1) -OS(O)₂CF₃,
- (2) -OS(O)₂F,
- (3) -OS(O)₂R^{21a} wherein R^{21a} is loweralkyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl,

45 (4) -OC(O)R²³ wherein R²³ is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclicalkyl, alkoxy, -O-cycloalkyl, -O-aryl, -O-heterocyclic, -O-(N-succinimidyl) or 5-tetrazolyl;
(5) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from

50 (a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,
(e) cycloalkyl,

55 (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is

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substituted by one or two substituents independently selected from

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- (1) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- 95 (6) -OR²⁵ wherein R²⁵ is as defined above,
- (7) a protected hydroxy group,
- (8) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- (9) -O(CH₂)_iC(O)OR²⁰ wherein i is one or two and R²⁰ is independently defined as above,
- 100 (10) -O(CH(Si(CH₃)₃))-(CH₂)_jC(O)OR²⁰ wherein j is zero or one and R²⁰ is independently defined as above,
- (11) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (12) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- 105 (13) -O(CH₂)_iC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
- (14) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- 110 (15) -O(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (16) -O(CH₂)_iNHC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
- (17) -OS(O)₂N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- 115 (18) -O(CH₂)_i-NHC(O)R²⁴ wherein R²⁴ is defined as above,
- (19) -OCH(R²⁴)-SH wherein R²⁴ is defined as above,
- (20) -OCH(R²⁴)-S-loweralkyl wherein R²⁴ is defined as above,
- (21) -OCH(R²⁴)-S-aryl wherein R²⁴ is defined as above and
- (22) -N₃;
- 120 R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy,

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125 alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;
130 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

2. A compound according to Claim 1 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is hydrogen;
R⁹ is defined as above;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
10 X and Y taken together are oxo.

3. A compound according to Claim 1 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
(1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl,
cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
10 heterocyclalkyl, each of which is optionally substituted with loweralkyl,
halogen, hydroxy, aryl or heterocyclic; or

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- (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- 15 R⁸ is hydrogen;
 R⁹ is
 (1) -OH,
 (2) -OC(O)R²³ wherein R²³ is -O-aryl, -O-(N-succinimidyl), -O-benzotriazolyl, -O-2'-pyridyl or 5-tetrazolyl,
20 (3) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from
 (a) hydrogen,
 (b) loweralkyl,
 (c) alkenyl,
25 (d) alkynyl,
 (e) cycloalkyl,
 (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
 (i) hydroxy,
 (ii) -COOH,
 (iii) -CN,
 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
35 R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
 (v) cycloalkyl,
 (vi) aryl,
 (vii) heterocyclic,
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- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,

(ix) guanidino,

(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,

(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,

(xii) -SO₃H,

(xiii) -S(O)₂NH₂,

(xiv) -SR²⁸ wherein R²⁸ is defined as above,

(xv) halogen,

(xvi) oxo and

(xvii) epoxy;

(g) aryl,

(h) heterocyclic,

(i) -NHC(O)-O-loweralkyl,

(j) -NHC(O)-aryl,

(k) -NHC(O)-heterocyclic and

(l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,

(4) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,

(5) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are defined as above,

(6) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,

(7) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above or

(8) -O(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above;

R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and

X and Y taken together are oxo.

4. A compound according to Claim 1 wherein

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

R⁴ and R⁵ taken together are oxo;

5 R⁶ and R⁷ taken together are

(1) oxo,

(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

10 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

15 R⁹ is

(1) -OH,

(2) -OC(O)R²³ wherein R²³ is -O-aryl, -O-(N-succinimidyl), -O-benzotriazolyl, -O-2'-pyridyl or 5-tetrazolyl,

20 (3) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from

(a) hydrogen,

(b) loweralkyl,

(c) alkenyl,

(d) alkynyl,

25 (e) cycloalkyl,

(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

30 (i) hydroxy,

(ii) -COOH,

(iii) -CN,

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- 35 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 40 (v) cycloalkyl,
- (vi) aryl,
- (vii) heterocyclic,
- (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 45 (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- 50 (xiii) -S(O)₂NH₂,
- (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- (xv) halogen,
- (xvi) oxo and
- (xvii) epoxy;
- 55 (g) aryl,
- (h) heterocyclic,
- (i) -NHC(O)-O-loweralkyl,
- (j) -NHC(O)-aryl,
- (k) -NHC(O)-heterocyclic and
- 60 (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- (4) -OC(O)N(OR²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above,
- 65 (5) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein iis one or two and R²⁴ and R²⁵ are defined as above,

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(6) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,

70 (7) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above or

(8) -O(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above;

R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

75

5. A compound according to Claim 1 wherein

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

R⁴ and R⁵ taken together are oxo;

5 R⁶ and R⁷ taken together are oxo;

R⁸ is hydrogen;

R⁹ is -OH, -O-loweralkyl or -OC(O)N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above;

R^{10a} is methoxy and R^{10b} is hydrogen; and

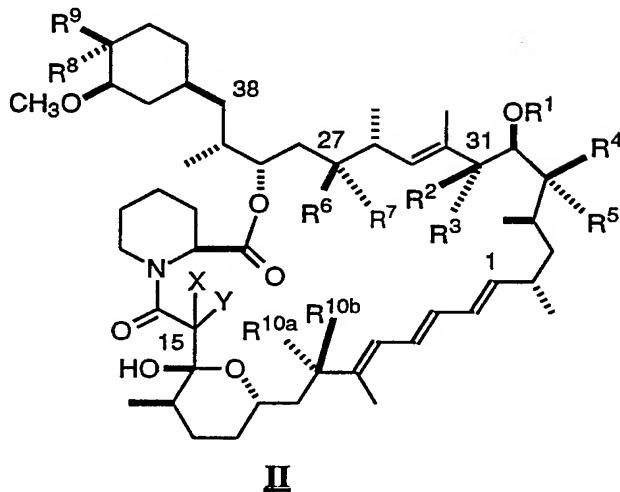
10 X and Y taken together are oxo.

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6. A compound of the formula:



- 5 wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

- 10 R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

- 15 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

- (1) oxo,
- (2) diazo,
- 20 (3) =CH₂,
- (4) -O-(CH₂)₂-O-,
- (5) -S-(CH₂)₂-S-,
- (6) -O-(CH₂)₃-O-,
- (7) -S-(CH₂)₃-S-,

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- 25 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
30 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

35 R⁹ is

- (1) -SR²⁴ wherein R²⁴ is
(a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
40 (d) alkynyl,
(e) cycloalkyl,
(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
45 (i) hydroxy,
(ii) -COOH,
(iii) -CN,
(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
50 R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
(v) cycloalkyl,
55 (vi) aryl,

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7. A compound according to Claim 6 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is hydrogen;
R⁹ is -SR²⁴ wherein R²⁴ is defined as above;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
10 X and Y taken together are oxo.

8. A compound according to Claim 6 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
 (1) oxo,
 (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl,
 cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
10 heterocyclicalkyl, each of which is optionally substituted with loweralkyl,
 halogen, hydroxy, aryl or heterocyclic; or
 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and
 heterocyclicalkyl;
15 R⁸ is hydrogen;
R⁹ is -SR²⁴ wherein R²⁴ is hydrogen, loweralkyl, substituted loweralkyl as
defined above, aryl or heterocyclic;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
X and Y taken together are oxo.

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9. A compound according to Claim 6 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
5 R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are oxo;
R⁸ is hydrogen;
R⁹ is -SR²⁴ wherein R²⁴ is hydrogen, loweralkyl, substituted loweralkyl as
defined above, aryl or heterocyclic;
10 R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

10. A compound according to Claim 6 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
5 R⁶ and R⁷ taken together are oxo;
R⁸ is hydrogen;
R⁹ is -SR²⁴ wherein R²⁴ is hydrogen, imidazol-2-yl or N-methyl-imidazol-2-yl;
R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

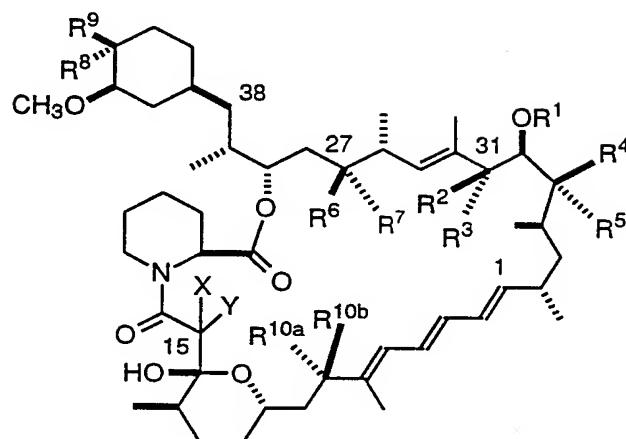
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11. A compound of the formula:



III

5 wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

10 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

15 R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

20 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

(1) oxo,

(2) diazo,

(3) =CH₂

(4) -O-(CH₂)₂-O-,

(5) -S-(CH₂)₂-S-,

(6) -O-(CH₂)₃-O-,

(7) -S-(CH₂)₃-S-,

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- 25 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
30 (9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is hydrogen;

- 35 R⁹ is
(1) -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from
(a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
40 (d) alkynyl,
(e) cycloalkyl,
(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
45 (i) hydroxy,
(ii) -COOH,
(iii) -CN,
(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
50 R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
55 (v) cycloalkyl,
(vi) aryl,

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- (vii) heterocyclic,
60 (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
(ix) guanidino,
65 (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
(xii) -SO₃H,
70 (xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
(xvi) oxo and
(xvii) epoxy;
- (g) aryl,
(h) heterocyclic,
75 (i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,
(k) -NHC(O)-heterocyclic and
(l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl,
(2) -N=C=O,
(3) -NHC(O)-R* or
80 (4) -NHS(O)₂-R* wherein R* is
(a) loweralkyl,
(b) cycloalkyl,
(c) aryl,
(d) heterocyclic,
85 (e) loweralkyl substituted by one or two substituents independently selected from
(i) hydroxy,
(ii) -COOH,
(iii) -CN,

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- 90 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 95 (v) cycloalkyl,
- (vi) aryl,
- (vii) heterocyclic,
- 100 (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- (ix) guanidino,
- (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
- 105 (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
- (xii) -SO₃H,
- (xiii) -S(O)₂NH₂,
- (xiv) -SR²⁸ wherein R²⁸ is defined as above,
- (xv) halogen,
- 110 (xvi) oxo and
- (xvii) epoxy;
- (f) -N(R^a)(R^b) wherein R^a and R^b are independently selected from hydrogen, loweralkyl and -N(R^c)(R^d) wherein R^c and R^d are independently selected from hydrogen and loweralkyl or
- 115 (g) -OR* wherein R* is defined as above;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

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X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen
125 and X is hydroxy or protected hydroxy or X and Y taken together are oxo;
or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

12. A compound according to Claim 11 wherein

R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
5 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is hydrogen;
R⁹ is -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are defined as above;
10 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
X and Y taken together are oxo.

13. A compound according to Claim 11 wherein

R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
(1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl,
cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
10 heterocyclicalkyl, each of which is optionally substituted with loweralkyl,
halogen, hydroxy, aryl or heterocyclic; or
(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and
heterocyclicalkyl;
15 R⁸ is hydrogen;
R⁹ is -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from
hydrogen, loweralkyl, substituted loweralkyl as defined above,

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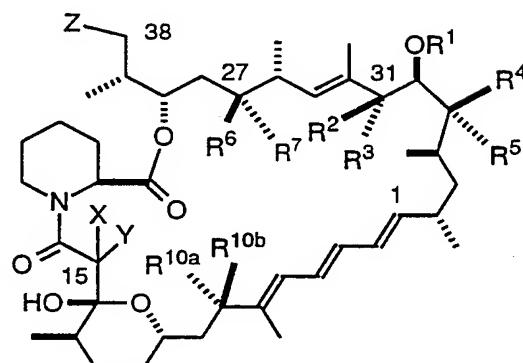
- NHC(O)-O-loweralkyl, -NHC(O)-aryl and -NHC(O)-heterocyclic or R²⁴ and R²⁵ taken together form a heterocyclic ring;
- 20 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

14. A compound according to Claim 11 wherein
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- 5 R⁶ and R⁷ taken together are oxo;
- R⁸ is hydrogen;
- R⁹ is -N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected from hydrogen, loweralkyl, substituted loweralkyl as defined above,
- NHC(O)-O-loweralkyl, -NHC(O)-aryl and -NHC(O)-heterocyclic or R²⁴ and
- 10 R²⁵ taken together form a heterocyclic ring;
- R^{10a} is methoxy and R^{10b} is hydrogen; and X and Y taken together are oxo.

15. A compound according to Claim 11 wherein
- R¹ is methyl;
- R² is hydrogen and R³ is hydroxy;
- R⁴ and R⁵ taken together are oxo;
- 5 R⁶ and R⁷ taken together are oxo;
- R⁸ is hydrogen;
- R⁹ is -NH₂, 2-pyridon-1-yl or 4-pyridon-1-yl;
- R^{10a} is methoxy and R^{10b} is hydrogen; and
- X and Y taken together are oxo.

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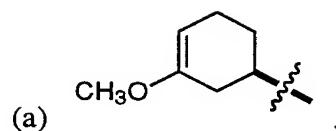
16. A compound of the formula:



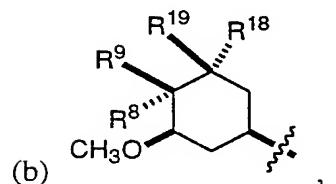
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IV

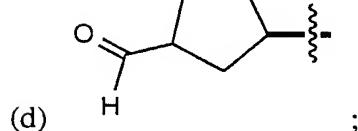
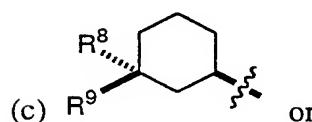
wherein Z is



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- 20 R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;
- 25 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;
- 30 R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;
- 35 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are
(1) oxo,
(2) diazo,
(3) =CH₂
(4) -O-(CH₂)₂-O-,
(5) -S-(CH₂)₂-S-,
(6) -O-(CH₂)₃-O-,
(7) -S-(CH₂)₃-S-,
- 40 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;
- 45 R⁸, R⁹, R¹⁸ and R¹⁹ are independently selected from
(1) hydrogen,
(2) -OS(O)₂CF₃,
(3) -OS(O)₂F,

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- (4) -OS(O)₂R^{21a} wherein R^{21a} is loweralkyl, aryl, arylalkyl, heterocyclic or heterocyclalkyl,
55 (5) -OC(O)R²³ wherein R²³ is -O-aryl, -O-(N-succinimidyl),
-O-benzotriazolyl, -O-2'-pyridyl or 5-tetrazolyl;
(6) -OC(O)-N(R²⁴)(R²⁵) wherein R²⁴ and R²⁵ are independently selected
from
60 (a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,
(e) cycloalkyl,
(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl
65 or substituted cycloalkyl wherein the loweralkyl group, the
alkenyl group, the alkynyl group or the cycloalkyl group is
substituted by one or two substituents independently selected from
(i) hydroxy,
(ii) -COOH,
(iii) -CN,
70 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic
or -Q-(heterocyclalkyl) wherein Q is -O-, -S-, -S(O)-,
-S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-,
-O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,
-NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-,
75 -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
(v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
80 (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently
selected from hydrogen, loweralkyl, hydroxyalkyl, aryl
and heterocyclic,
(ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,

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- (17) $-\text{O}(\text{CH}_2)_i\text{NHC(O)N(R}^{24}\text{)(N(R}^{24}\text{)(R}^{25}\text{)})$ wherein i, R²⁴ and R²⁵ are defined as above,
- 120 (18) $-\text{OS(O)}_2\text{N(R}^{24}\text{)(R}^{25}\text{)}$ wherein R²⁴ and R²⁵ are defined as above,
- (19) $-\text{O}(\text{CH}_2)_i\text{-NHC(O)R}^{24}$ wherein R²⁴ is defined as above,
- (20) $-\text{OCH(R}^{24}\text{)-SH}$ wherein R²⁴ is defined as above,
- (21) $-\text{OCH(R}^{24}\text{)-S-loweralkyl}$ wherein R²⁴ is defined as above,
- (22) $-\text{OCH(R}^{24}\text{)-S-aryl}$ wherein R²⁴ is defined as above,
- 125 (23) $-\text{N}_3$,
- (24) $-\text{N=C=O}$,
- (25) $-\text{N(R}^{24}\text{)(R}^{25}\text{)}$ wherein R²⁴ and R²⁵ are defined as above,
- (26) $-\text{NHC(O)-R}^{24}$ wherein R²⁴ is defined as above,
- (27) $-\text{NHC(O)-N(R}^{24}\text{)(R}^{25}\text{)}$ wherein R²⁴ and R²⁵ are defined as above,
- 130 (28) $-\text{S-R}^{24}$ wherein R²⁴ is defined as above and
- (29) $-\text{S-q-R}^{24}$ wherein q is a divalent radical selected from the group consisting of $-\text{S-}$, $-\text{C(O)-}$, $-\text{C(O)-O-}$, $-\text{C(O)-NH-}$ and $-\text{C(N(R}^{27}\text{))-NHNH-}$ and R²⁴ and R²⁷ are defined as above,
- with the proviso that one of R⁸ and R⁹ is hydrogen and the other is not hydrogen and one of R¹⁸ and R¹⁹ is hydrogen and the other is not hydrogen; or
- 135 R⁸ and R⁹ taken together are
- (1) oxo,
- (2) $=\text{N-O-R}^{24}$ wherein R²⁴ is defined as above or
- 140 (3) $=\text{N-N(R}^{24}\text{)(R}^{25}\text{)}$ wherein R²⁴ and R²⁵ are defined as above; or
- R¹⁸ and R¹⁹ taken together are
- (1) oxo,
- (2) $=\text{N-O-R}^{24}$ wherein R²⁴ is independently defined as above or
- 145 (3) $=\text{N-N(R}^{24}\text{)(R}^{25}\text{)}$ wherein R²⁴ and R²⁵ are independently defined as above; or
- one of R⁸ and R⁹ taken together with one of R¹⁸ and R¹⁹ form a heterocyclic ring with the others of R⁸, R⁹, R¹⁸ and R¹⁹ being hydrogen or together forming a bond; or
- R⁸ and R¹⁸ are hydrogen and R^{8'} and R¹⁹ form a bond;
- 150

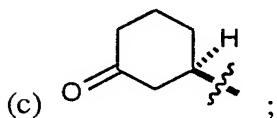
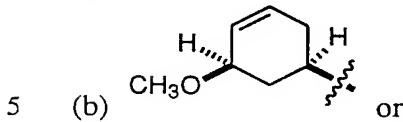
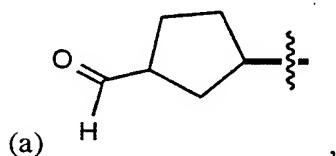
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R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

160 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

17. A compound according to Claim 16 wherein
Z is



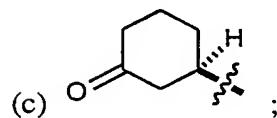
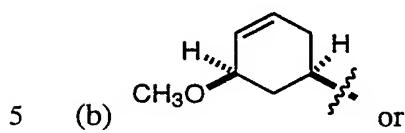
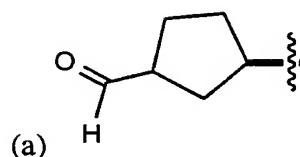
R¹ is methyl;

10 R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and

15 X and Y taken together are oxo.

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18. A compound according to Claim 16 wherein
Z is

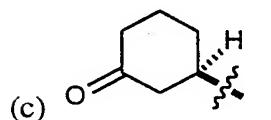
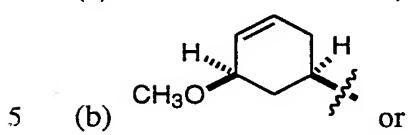
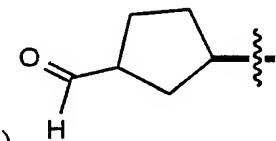


- 10 R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
- 15 (1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;
- 20 R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
X and Y taken together are oxo.

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19. A compound according to Claim 16 wherein

Z is



10 R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ taken together are

(1) oxo,

15 (2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected

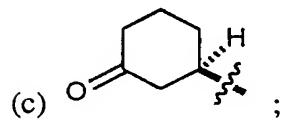
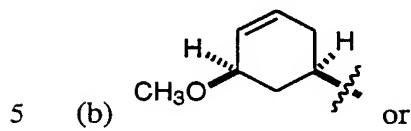
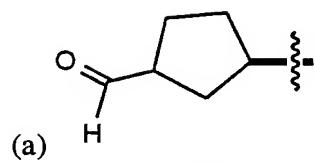
20 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R^{10a} is methoxy and R^{10b} is hydrogen; and

X and Y taken together are oxo.

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20. A compound according to Claim 16 wherein
Z is



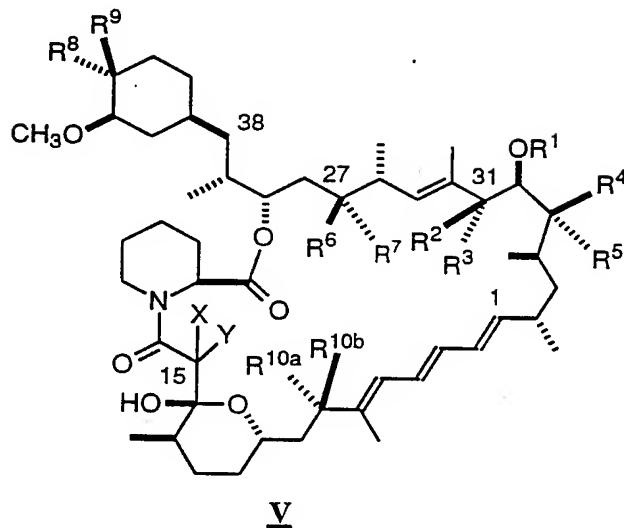
- 10 R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
R⁶ and R⁷ taken together are oxo;
R^{10a} is methoxy and R^{10b} is hydrogen; and
15 X and Y taken together are oxo.

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21. A compound of the formula:



5 wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

10 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R₅ taken together are oxo;

15 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

- (1) oxo,
- (2) diazo,
- 20 (3) =CH₂,
- (4) -O-(CH₂)₂-O-,
- (5) -S-(CH₂)₂-S-,
- (6) -O-(CH₂)₃-O-,

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- 25 (7) $-\text{S}-(\text{CH}_2)_3-\text{S}-$,
(8) $=\text{N}-\text{OR}^{20}$ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
30 (9) $=\text{N}-\text{N}(\text{R}^{21})(\text{R}^{22})$ wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is

- 35 (1) -OC(O)N(OR²⁰)(R²⁴) or
(2) -O-C(O)-NHN(R²⁴)(R²⁵)
wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl or heterocyclic, each of which is optionally substituted with loweralkyl, hydroxy, aryl or heterocyclic and R²⁴ and R²⁵ are independently selected from

40 (a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,
45 (e) cycloalkyl,
(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

50 (i) hydroxy,
(ii) -COOH,
(iii) -CN,
(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,

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- NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-,
-N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 60 (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
(viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently
selected from hydrogen, loweralkyl, hydroxyalkyl, aryl
and heterocyclic,
- 65 (ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
(xii) -SO₃H,
70 (xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
(xvi) oxo and
(xvii) epoxy;
- 75 (g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,
(k) -NHC(O)-heterocyclic or
- 80 (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is
carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing
heterocyclic group;
- 85 R⁹ is hydrogen;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy,
alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as
above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy,

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- 90 alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and
X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen
95 and X is hydroxy or protected hydroxy or X and Y taken together are oxo;
or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

22. A compound according to Claim 21 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is defined as above;
R⁹ is hydrogen;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen;
10 R²⁰ is defined as above;
R²⁴ is defined as above; and
X and Y taken together are oxo.

23. A compound according to Claim 21 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R₅ taken together are oxo;
R⁶ and R⁷ taken together are
(1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl,
cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
10 heterocyclicalkyl, each of which is optionally substituted with loweralkyl,
halogen, hydroxy, aryl or heterocyclic; or

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(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;

15 R⁸ is -OC(O)N(OR²⁰)(R²⁴) wherein R²⁰ and R²⁴ are defined as above; R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

24. A compound according to Claim 21 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
5 R⁶ and R⁷ taken together are oxo;
R⁸ is -OC(O)N(OR²⁰)(R²⁴) wherein R²⁰ is hydrogen, loweralkyl or arylalkyl and R²⁴ is hydrogen, loweralkyl or cycloalkyl;
R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

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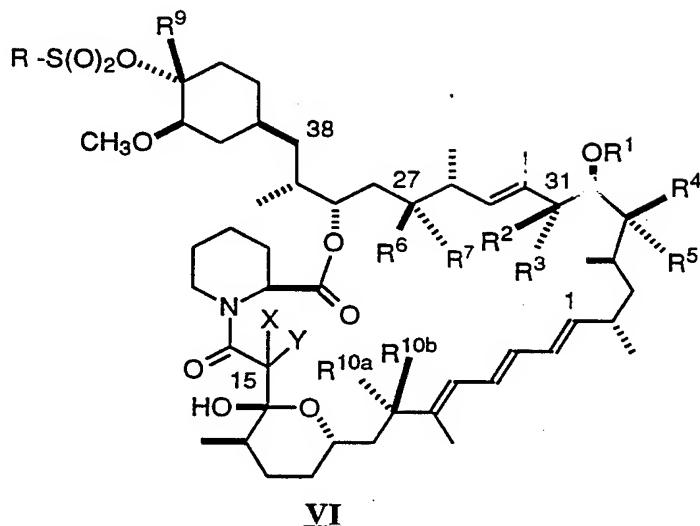
25. A compound according to Claim 21 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
5 R⁶ and R⁷ taken together are oxo;
R⁸ is -OC(O)N(OR²⁰)(R²⁴) wherein R²⁰ is hydrogen, methyl or benzyl and R²⁴ is hydrogen or methyl;
R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

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26. A compound of the formula:



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wherein R is F;

10 R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

15 R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

20 R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

25 R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

- (1) oxo,
- (2) diazo,
- (3) =CH₂
- (4) -O-(CH₂)₂-O-,

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- 25 (5) -S-(CH₂)₂-S-,
 (6) -O-(CH₂)₃-O-,
 (7) -S-(CH₂)₃-S-,
 (8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl,
 cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
 heterocyclalkyl, each of which is optionally substituted with loweralkyl,
 halogen, hydroxy, aryl or heterocyclic; or
 (9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
 from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and
 heterocyclalkyl;
- 30 R⁹ is hydrogen;
 R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy,
 alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as
 above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy,
 alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently
 defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is
 loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and
- 40 X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen
 and X is hydroxy or protected hydroxy or X and Y taken together are oxo;
 or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.
- 45 27. A compound according to Claim 26 wherein
 R is F;
 R¹ is methyl;
 R² is hydrogen and R³ is hydroxy;
 5 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
 R⁵ taken together are oxo;
 R⁶ and R⁷ are defined as above;

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R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

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28. A compound according to Claim 26 wherein

R is F;

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

5 R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ taken together are

(1) oxo,

(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or

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heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and

15

heterocyclicalkyl;

R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and X and Y taken together are oxo.

29. A compound according to Claim 26 wherein

R is F;

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

5 R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ taken together are

(1) oxo,

(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or

10

heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

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(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

- 15 R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

30. A compound according to Claim 26 wherein

R is F;

R¹ is methyl;

R² is hydrogen and R³ is hydroxy;

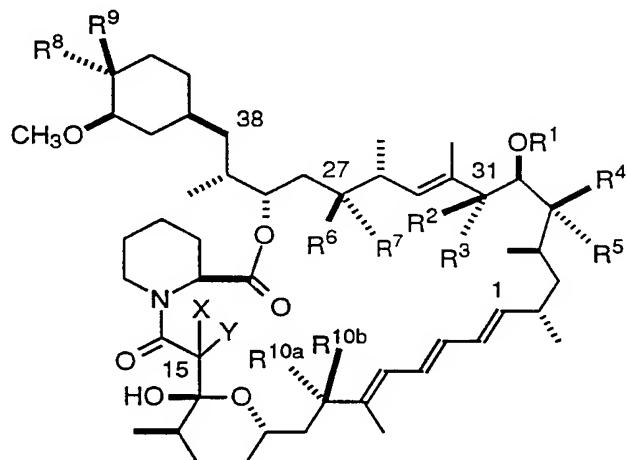
5 R⁴ and R⁵ taken together are oxo;

R⁶ and R⁷ taken together are oxo;

R^{10a} is methoxy and R^{10b} is hydrogen; and

X and Y taken together are oxo.

31. A compound of the formula:



VII

5 wherein R¹ is hydrogen, a hydroxy protecting group, loweralkyl or phenyl-substituted loweralkyl;

R² is hydrogen and R³ is hydroxy or protected hydroxy or R² and R³ taken together are oxo;

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R⁴ is hydrogen or phenyl-substituted loweralkyl and R⁵ is hydroxy or protected hydroxy or R⁵ is hydrogen or phenyl-substituted loweralkyl and R⁴ is hydroxy or protected hydroxy or R⁴ and R⁵ taken together are oxo;

15

R⁶ is hydrogen or phenyl-substituted loweralkyl and R⁷ is hydrogen, hydroxy or protected hydroxy or R⁷ is hydrogen or phenyl-substituted loweralkyl and R⁶ is hydroxy or protected hydroxy or R⁶ and R⁷ taken together are

(1) oxo,

(2) diazo,

20

(3) =CH₂

(4) -O-(CH₂)₂-O-,

(5) -S-(CH₂)₂-S-,

(6) -O-(CH₂)₃-O-,

(7) -S-(CH₂)₃-S-,

25

(8) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

30

(9) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected

from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R⁸ is

35

(1) -O(CH₂)_iC(O)OR²⁰ wherein i is one or two and R²⁰ is independently defined as above,

(2) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are independently selected from

(a) hydrogen,

(b) loweralkyl,

40

(c) alkenyl,

(d) alkynyl,

(e) cycloalkyl,

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- (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the
45 alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
(i) hydroxy,
(ii) -COOH,
(iii) -CN,
50 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
55 (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
60 (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
(ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
65 (xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
(xii) -SO₃H,
(xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
70 (xv) halogen,
(xvi) oxo and
(xvii) epoxy;
(g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
75 (j) -NHC(O)-aryl,
(k) -NHC(O)-heterocyclic and

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- (1) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- 80 (3) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (4) -O(CH₂)_iC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above,
- 85 (5) -O(CH₂)_iNHC(O)N(R²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
- (6) -(CH₂)_iNHC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above or
- (7) -(CH₂)_iNHC(O)N(R²⁴)(N(R²⁴)(R²⁵)) wherein i, R²⁴ and R²⁵ are defined as above;
- 90

R⁹ is hydrogen;

R^{10a} is hydrogen and R^{10b} is hydrogen, hydroxy, protected hydroxy, alkoxy, 95 alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10b} is hydrogen and R^{10a} is hydrogen, hydroxy, protected hydroxy, alkoxy, alkenyl, alkenyloxy, halogen or -SR²⁸ wherein R²⁸ is independently defined as above or R^{10a} and R^{10b} are both alkoxy or -SR^{28a} wherein R^{28a} is loweralkyl, aryl or heterocyclic or R^{10a} and R^{10b} taken together are oxo; and

100

X is hydrogen and Y is hydrogen, hydroxy or protected hydroxy or Y is hydrogen and X is hydroxy or protected hydroxy or X and Y taken together are oxo;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

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32. A compound according to Claim 31 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ are defined as above;
R⁸ is defined as above;
R⁹ is hdyrogen;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
10 X and Y taken together are oxo.

33. A compound according to Claim 31 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ is hydrogen and R⁵ is hydroxy or R⁵ is hydrogen and R⁴ is hydroxy or R⁴ and
5 R⁵ taken together are oxo;
R⁶ and R⁷ taken together are
(1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl,
cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or
10 heterocyclicalkyl, each of which is optionally substituted with loweralkyl,
halogen, hydroxy, aryl or heterocyclic; or
(3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected
from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and
heterocyclicalkyl;
15 R⁸ is
(1) -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵
are independently selected from
(a) hydrogen,
(b) loweralkyl,
20 (c) alkenyl,
(d) alkynyl,
(e) cycloalkyl,

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- (f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from
- 25 (i) hydroxy,
(ii) -COOH,
(iii) -CN,
30 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 35 (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
40 (viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
(ix) guanidino,
45 (x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
(xii) -SO₃H,
(xiii) -S(O)₂NH₂,
50 (xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
(xvi) oxo and
55 (xvii) epoxy;
- (g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,
(k) -NHC(O)-heterocyclic and

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- (1) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group or
60 (2) -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i, R²⁴ and R²⁵ are defined as above,
R⁹ is hydrogen;
R^{10a} is hydrogen, methoxy or fluoro and R^{10b} is hydrogen; and
65 X and Y taken together are oxo.

34. A compound according to Claim 31 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
5 R⁶ and R⁷ taken together are
(1) oxo,
(2) =N-OR²⁰ wherein R²⁰ is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or
10 (3) =N-N(R²¹)(R²²) wherein R²¹ and R²² are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalalkyl;
R⁸ is -O(CH₂)_iC(O)N(R²⁴)(R²⁵) wherein i is one or two and R²⁴ and R²⁵ are
15 independently selected from
(a) hydrogen,
(b) loweralkyl,
(c) alkenyl,
(d) alkynyl,
20 (e) cycloalkyl,
(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the

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alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

- 25 (i) hydroxy,
(ii) -COOH,
(iii) -CN,
(iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic
or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-,
-S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-,
-O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,
-NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-,
-N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein
R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 30 (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
(viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently
selected from hydrogen, loweralkyl, hydroxyalkyl, aryl
and heterocyclic,
- 35 (ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
(xii) -SO₃H,
40 (xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
(xvi) oxo and
(xvii) epoxy;
- 45 (g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,
(k) -NHC(O)-heterocyclic and
50 (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is
carboxyalkyl
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or $-N(R^{24})(R^{25})$ taken together form a nitrogen-containing heterocyclic group,

R^9 is hydrogen;

60 R^{10a} is methoxy and R^{10b} is hydrogen; and
 X and Y taken together are oxo.

35. A compound according to Claim 31 wherein

R^1 is methyl;

R^2 is hydrogen and R^3 is hydroxy;

R^4 and R^5 taken together are oxo;

5 R^6 and R^7 taken together are

(1) oxo,

(2) $=N-OR^{20}$ wherein R^{20} is hydrogen, loweralkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkenyl, aryl, arylalkyl, heterocyclic or heterocyclicalkyl, each of which is optionally substituted with loweralkyl, halogen, hydroxy, aryl or heterocyclic; or

10 (3) $=N-N(R^{21})(R^{22})$ wherein R^{21} and R^{22} are independently selected from hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic and heterocyclicalkyl;

R^8 is $-O(CH_2)_iC(O)N(OR^{24})(R^{25})$ wherein i is one or two and R^{24} and R^{25} are

15 independently selected from

(a) hydrogen,

(b) loweralkyl,

(c) alkenyl,

(d) alkynyl,

20 (e) cycloalkyl,

(f) substituted loweralkyl, substituted alkenyl, substituted alkynyl or substituted cycloalkyl wherein the loweralkyl group, the alkenyl group, the alkynyl group or the cycloalkyl group is substituted by one or two substituents independently selected from

25 (i) hydroxy,

(ii) $-COOH$,

(iii) $-CN$,

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- 30 (iv) -Q-loweralkyl, -Q-aryl, -Q-(arylalkyl), -Q-heterocyclic or -Q-(heterocyclicalkyl) wherein Q is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, -S(O)₂NH-, -NHS(O)₂-, -N(R²⁷)-, -C(NR²⁷)NHNH- and -NHNHC(NR²⁷)- wherein R²⁷ is hydrogen, loweralkyl, aryl or heterocyclic,
- 35 (v) cycloalkyl,
(vi) aryl,
(vii) heterocyclic,
(viii) -N(R²⁸)(R²⁹) wherein R²⁸ and R²⁹ are independently selected from hydrogen, loweralkyl, hydroxyalkyl, aryl and heterocyclic,
- 40 (ix) guanidino,
(x) -S(O)₂R¹¹ wherein R¹¹ is loweralkyl, aryl or arylalkyl,
(xi) -OS(O)₂R¹¹ wherein R¹¹ is defined as above,
(xii) -SO₃H,
45 (xiii) -S(O)₂NH₂,
(xiv) -SR²⁸ wherein R²⁸ is defined as above,
(xv) halogen,
(xvi) oxo and
(xvii) epoxy;
- 50 (g) aryl,
(h) heterocyclic,
(i) -NHC(O)-O-loweralkyl,
(j) -NHC(O)-aryl,
(k) -NHC(O)-heterocyclic and
- 55 (l) loweralkyl substituted by -OC(O)-R^f wherein R^f is carboxyalkyl
or -N(R²⁴)(R²⁵) taken together form a nitrogen-containing heterocyclic group,
- R⁹ is hydrogen;
- 60 R^{10a} is methoxy and R^{10b} is hydrogen; and
X and Y taken together are oxo.

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36. A compound according to Claim 31 wherein
R¹ is methyl;
R² is hydrogen and R³ is hydroxy;
R⁴ and R⁵ taken together are oxo;
5 R⁶ and R⁷ taken together are oxo;
R⁸ is -O(CH₂)_iC(O)N(OR²⁴)(R²⁵) wherein i is one or two and R²⁴ is hydrogen,
loweralkyl or arylalkyl and R²⁵ is hydrogen, loweralkyl or cycloalkyl;
R⁹ is hydrogen;
R^{10a} is methoxy and R^{10b} is hydrogen; and
10 X and Y taken together are oxo.

37. A pharmaceutical composition for immunomodulatory treatment comprising a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

38. A method of immunomodulatory treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 1.

39. A pharmaceutical composition for immunomodulatory treatment comprising a compound according to Claim 6 in combination with a pharmaceutically acceptable carrier.

40. A method of immunomodulatory treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 6.

41. A pharmaceutical composition for immunomodulatory treatment comprising a compound according to Claim 11 in combination with a pharmaceutically acceptable carrier.

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42. A method of immunomodulatory treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 11.

43. A pharmaceutical composition for immunomodulatory treatment comprising a compound according to Claim 16 in combination with a pharmaceutically acceptable carrier.

44. A method of immunomodulatory treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 16.

45. A pharmaceutical composition for immunomodulatory treatment comprising a compound according to Claim 21 in combination with a pharmaceutically acceptable carrier.

46. A method of immunomodulatory treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 21.

47. A pharmaceutical composition for immunomodulatory treatment comprising a compound according to Claim 31 in combination with a pharmaceutically acceptable carrier.

48. A method of immunomodulatory treatment comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 31.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 94/12777

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/18 A61K31/445 A61K31/395 // (C07D498/18, 311:00,
221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 18043 (AMERICAN HOME PROD) 16 September 1993 see claim 1 ---	1-5, 16-20, 37
X	WO,A,93 11130 (SMITHKLINE BEECHAM PLC) 10 June 1993 see claim 1 ---	1-37
Y	WO,A,92 05179 (AMERICAN HOME PROD) 2 April 1992 see claim 1 ---	1-37
Y	WO,A,92 21341 (PFIZER) 10 December 1992 see claim 1 ---	1-5, 16-25, 31-37
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

4 April 1995

Date of mailing of the international search report

- 3. 05. 95

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Authorized officer

Stellmach, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 258 389 (GOULET MARK ET AL) 2 November 1993 see claim 1 ---	1-37
X	US,A,5 260 300 (HU DAVID C) 9 November 1993 * & WO-A-94/11 380 * see claim 1 ---	1-37
X	US,A,5 262 423 (KAO WENLING) 16 November 1993 * & WO-A-94/10176 * see claim 1 ---	1-37
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X	US,A,5 151 413 (CAUFIELD CRAIG E ET AL) 29 September 1992 see claim 1 ---	1-37
X	US,A,5 100 883 (SCHIEHSER GUY A) 31 March 1992 see claim 1 ---	1-37
Y	EP,A,0 515 140 (AMERICAN HOME PROD) 25 November 1992 see claim 1 ---	1-37
Y	EP,A,0 509 795 (AMERICAN HOME PROD) 21 October 1992 see claim 1 ---	1-37
Y	EP,A,0 507 556 (AMERICAN HOME PROD) 7 October 1992 see claim 1 ---	1-37
Y	EP,A,0 470 804 (AMERICAN HOME PROD) 12 February 1992 see claim 1 ---	16
Y	EP,A,0 429 436 (UNIV KANSAS) 29 May 1991 see claim 1 ---	1-37
P,X	EP,A,0 593 227 (AMERICAN HOME PROD) 20 April 1994 see claim 1 ---	1-37
P,X	WO,A,94 02137 (SMITHKLINE BEECHAM CORP ; HOLT DENNIS ALAN (US); LUENGO JUAN IGNACI) 3 February 1994 see claim 1 ---	1-37
		-/-

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 94/12777

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,94 02485 (SMITHKLINE BEECHAM CORP ;HOLT DENNIS ALAN (US); LUENGO JUAN IGNACIO) 3 February 1994 see claim 1 ---	1-37
P,X	WO,A,94 04540 (AMERICAN HOME PROD) 3 March 1994 see claim 1 ---	1-37
P,X	WO,A,94 09010 (SANDOZ AG ;SANDOZ AG (DE); SANDOZ LTD (CH); COTTENS SYLVAIN (CH);) 28 April 1994 see claim 1 ---	1-37
P,X	WO,A,94 02136 (SMITHKLINE BEECHAM CORP ;LUENGO JUAN IGNACIO (US)) 3 February 1994 see claim 1 -----	1-37

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 38-48 are directed to a method of treatment of the human/animal body (Rule 39.1.(iv)), the search has been carried out and based on the alleged effects of the compounds.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat	Application No
PCT/US	94/12777

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Internat	Application No
PCT/US 94/12777	

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